

Posters 2

Monday, August 9
17:40 – 19:00

- P2-1 MEG: Language
- P2-2 Fetal MCG
- P3-3 Fetal and perinatal MEG
- P4-4 Cardiac modeling
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Neuromagnetic Signatures of Verbs

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ABSTRACT

In language, verbs play an important role for understanding and generating sentences. Like in a theatre, verbs describe a scene and define who of the many players plays which role. Here we demonstrate neuromagnetic brain reflections of the verb's so-called argument structure (the number of players). 22 Subjects read 390 isolated verbs requiring one (like snored in "Peter snored."), two ("Mary saw John.") or three obligatory arguments ("Paul gave Kim the book.") and were instructed to press a button after randomly interspersed nouns. Brain activity 250 ms after stimulus-onset localized in the left temporal cortex significantly distinguished the number of arguments. Moreover, we were able to dissociate the verb's representation from the processing of its argument structure: presenting the same verbs after a name (one argument: "Peter snored", two arguments: "Mary solved", three arguments: "Paul gave") led to a significantly earlier peak-latency for grammatically complete (one argument: 397ms) than incomplete sentences (two arguments: 414ms and three arguments: 412ms). In contrast to the different levels of left temporal activation after isolated verbs, the processing of verbs within a context activated areas in the left inferior frontal gyrus.

KEY WORDS

Language, Syntax, Semantics, Verbs, Minimum Norm Estimate (MNE), Temporal Lobe, Inferior Frontal Gyrus (IFG).

INTRODUCTION

When we read or listen to sentences, verbs guide our understanding of the sentence's meaning as well as our automatic impression, as to whether the sentence is grammatically correct or not. In semantic terms, verbs describe 'scenes' [Tesnière, 1959] with one or more acting 'players' (human beings, animals or objects). The verb's argument structure defines how many players are needed to form a complete scene. In syntactic terms, the scene together with the players forms a sentence [Fillmore, 1966].

In this study we examined the cortical processing of verbs' argument structures. First, we compared cortical responses evoked by isolated verbs that varied in their argument structure. Second, we examined the impact of syntactic context on this cortical verb processing by presenting the same verbs together with a name that filled the first position of the argument structure.

If the number of the verbs' arguments were distinctly represented in the mental lexicon, the amplitude of the magnetic evoked response to verbs of different argument structure should vary between the number of obligatory arguments. We hypothesized that this variation should be prominent in an anterior part of the left temporal lobe, the brain's primary storage for scenes⁴.

In contrast, presenting verbs in minimal grammatical context together with a name should activate areas known to be involved in syntactic processing. This minimal context would automatically activate the evaluation, whether the name-verb pair constituted a grammatically correct, complete sentence (as for verbs with one argument) or an incomplete and, hence, incorrect sentence (as for verbs with two or three obligatory arguments). Thus, we hypothesized that this syntactic processing of the name-verb combination produces differences in evoked magnetic responses in the left inferior frontal gyrus.

METHODS

In the preparatory study a list of 600 verbs with different argument-structures was selected from the CELEX-database [Baayan et al. 1993] and presented to 10 subjects with the instruction to generate a sentence for each verb. Verbs, for which the correct argument structure was generated in more than 70% of the generated sentences were selected for the MEG-study. They were assigned to three sets (one, two, three argument verbs) each containing 130 verbs in third person, singular, present, active form. The sets were matched for length (mean: 7.8 letters) and frequency (mean: 2.3 per million words, [Baayan et al. 1993]).

In the MEG-study, stimuli were presented to 22 healthy right-handed subjects (native speakers of German, 11 female, mean age: 24 years) naïve to the experimental purpose (as assessed by interrogation after the experiment). Stimuli were presented in white upper case letters (maximum word size 9x3 cm) on a black background at a distance of 1.4m using an LCD-projector situated outside the MEG chamber. In the first condition, verbs of all three sets were presented for 150ms in pseudo-random order with a variable inter-stimulus interval of 1200-2000ms. In the second condition, names preceded verbs for 150ms at a fixed interval of 500ms.

Subjects were instructed to fixate a cross which was projected on the screen during stimulus-free intervals. Sustained attention and access to the mental lexicon was ensured in both conditions subjects by requiring subjects to respond to nouns (derived from the verbs, but uniquely identifiable as nouns), which we interspersed with 10% probability.

Neuromagnetic signals were recorded continuously with a 148 channel whole head magnetometer (Magnes 2500 WH, 4D NeuroImaging Inc., San Diego) using a 0.1-100 Hz band-pass filter and sampled at a rate of 508 Hz. Additionally, vertical and horizontal EOG (electro-oculogram) were recorded for artefact control.

After external global noise subtraction continuous MEG data were split into epochs of 900ms length (100ms pre-stimulus) excluding contaminated epochs (EOG level > 100 μ V, an MEG level > 5 pT, button press). This resulted in a maximum of 130 MEG-traces per stimulus class and per subject. For each subject and for each of the 3 classes, stimulus-triggered evoked magnetic fields (EMFs) were calculated relative to a baseline of 100ms pre-stimulus onset. For these average EMFs, cortical sources were determined using the minimum norm estimate (MNE [Hämäläinen & Ilmoniemi, 1994]), an objective inverse method to reconstruct the topography of the primary current underlying a magnetic field distribution [Grave de Peralta Mendez 1997]. Cortical activity was approximated in a three-dimensional spherical source space of radius 10cm fitted individually to the head-shape of the subjects (4-D Neuroimaging software). On this sphere 197 equidistant dipoles for the estimation of source activity were assumed.

Topographies of the source activity averaged over 50ms windows were screened for obvious differences within conditions. Differences were obvious for the latency range 250ms-300ms (isolated verbs) and 350ms-450ms (names preceding verbs). For these two intervals, Regions of interest

were defined as the average strength of 6 dipoles a) over the left temporal lobe for the first condition and latency window and b) over the left inferior frontal gyrus including Broca's area for the second condition and latency window.

For statistical analyses, the average strength/amplitude of the six dipoles was calculated and the peak amplitude submitted to statistical analysis (condition without names). In the condition including names, the peak latency, not the peak amplitude was analyzed statistically. One-way repeated measures Analyses of Variance were calculated to assess significance of between-category differences. Linear trends and F-tests were used to further investigate significant main effects.

RESULTS

Figure 1 illustrates the influence of the argument structure on the brain response: The strength of sources evoked between 250 and 300ms in the left temporal lobe was largest (see white arrow in the map at the right hand corner) for verbs requiring one obligatory argument and smallest for verbs requiring three obligatory arguments. This is confirmed by a significant linear trend ($F(1,21) = 5.97$, $p = 0.023$). The main focus of the differential brain activity is indicated by the white arrow in figure 1a. The timeline of the brain's activity in this area illustrates the divergence of the waveforms starting around 250ms.

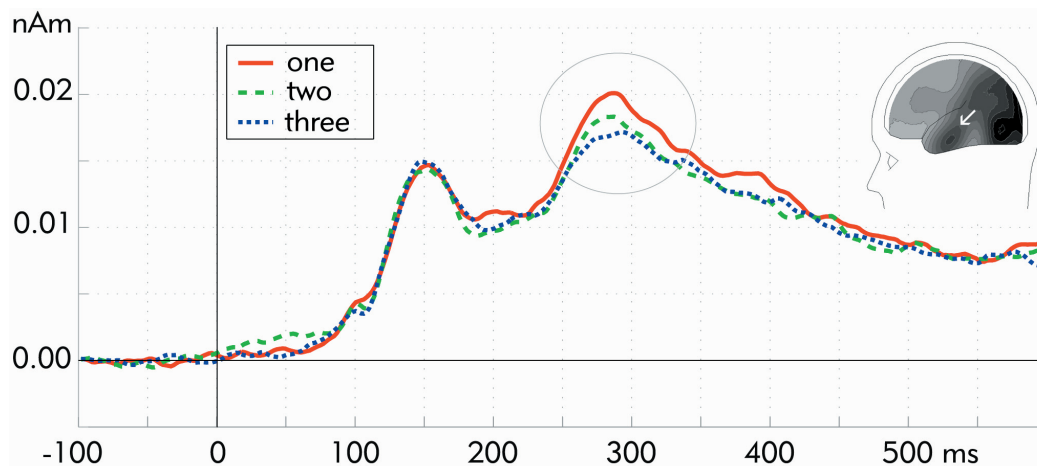


Figure 1. Brain activity (source strength) over time at the left temporal lobe (indicated by white arrow) for one, two and three argument verbs.

When verbs were presented in minimal syntactic contexts of names, evoked magnetic responses differed significantly around 400 ms after the verb's onset ($F(2,42) = 5.2$, $p = 0.009$, figure 2). Maximum activity in the left inferior frontal gyrus peaked significantly earlier, when the name-verb pair formed a complete, thus, grammatically correct sentence (mean peak latency: 397ms) compared to pairs forming incomplete sentences (mean peak latencies for verbs with two obligatory arguments: 414ms, with three arguments: 412ms, one vs two: $F(1,21) = 9.4$, $p = 0.005$; one vs three: $F(1,21) = 5.4$, $p = 0.029$; two vs three: n.s.).

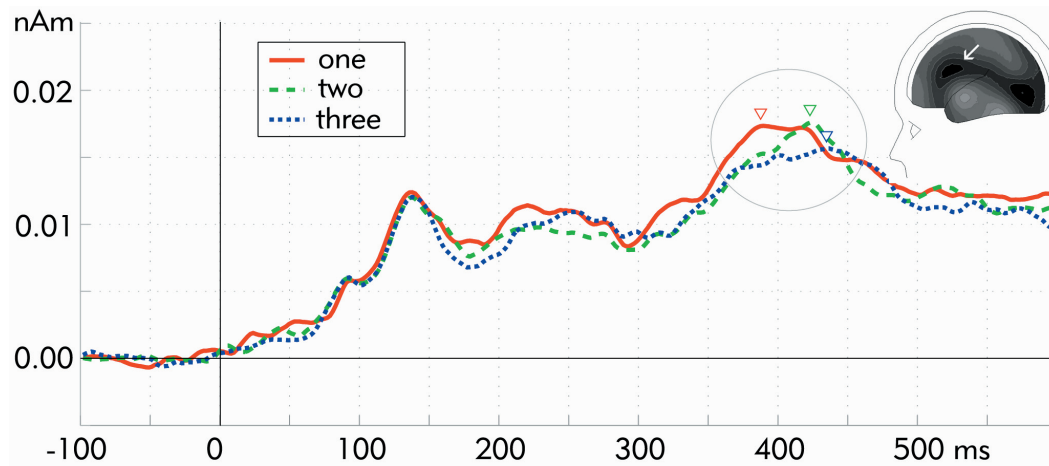


Figure 2. Brain activity (source strength) over time at the inferior frontal gyrus (indicated by white arrow) for one, two and three argument verbs following a name.

DISCUSSION

We found brain reflections of verb's argument structures. When a verb is presented in isolation, its argument structure reflected in an anterior part of the left temporal lobe. But when it is presented in a minimal syntactic context, the left inferior frontal gyrus is activated.

A simple, concrete feature like a word's length affects early brain responses produced by occipital lobe neurons [Tarkianen et al., 1999]. The word's frequency (how often a word is used in everyday language) is more abstract. Variation of word frequencies affects activation in more anterior parts of the left posterior temporal lobe [Assadollahi & Pulvermüller, 2003]. A verb's argument structure is an even more abstract linguistic feature. The left anterior temporal representation of the argument structure suggests that increasingly abstract features are processed in more anterior areas. Correspondingly, this is also found in the acoustic language processing domain: more anterior left temporal activation by higher levels of intelligibility of spoken sentences [Scott et al., 2000].

One might hypothesize that working memory capacity depends on the complexity of the expected sentence and, hence, on the verb's argument structure: increasing activity for an increasing number of verb's arguments. However, we observed the opposite dependence. Scenes may provide one

possible interpretation of the present effect. The brain's primary storage for scenes is the temporal lobe [Vandenberghe et al., 1996]. A scene consists of the meaning of the verb and one or more players taking part in the scene. The brain activates representations of scenes when a corresponding verb comes in. Most important is the recognition of the verb that describes the nature of the scene. Next, it is important to know who the players are. When a scene involves three players, the scene as a whole is not complete, as only one of four items is available. If in contrast, the verb needs only one player to complete a scene, the scene is much more complete, when one of two items is given. Thus, a representation of a scene is more strongly activated, when fewer players are required by the verb. The activation level in the temporal lobe may reflect the degree of completeness of a scene, therefore the corresponding activity is higher for one argument verbs than for three argument verbs.

Broca's area and surrounding parts in the left inferior frontal gyrus are involved in syntactic processing [Stromswold et al., 1996, Embick et al., 2000, Schwartz et al., 1980]. To us, the differential latency effect reflects that the processor finished building up the sentence representation earlier for the complete one-argument-verb-sentences whereas the processor waits for further words in the other conditions.

The present results suggest the following hypotheses:

- Activity from a single word progresses from the occipital lobe along the left temporal lobe almost to its pole.
- The corresponding representations of the word along the posterior/anterior axis become more complex and abstract.
- However, these representations are representations of the word without its context.
- The left inferior frontal gyrus is responsible for temporarily storing several such representations (like a name followed by a verb).
- Moreover, the left inferior frontal gyrus is able to match aspects of representations, such as the number, gender and case of a verb and a name, thereby
- building up a syntactic representation of the incoming stream of words.
- The activity peaks when a sentence is complete (one argument verbs in context of a name), but it is prolonged when the syntactic processor still has to wait for further input (two and three argument verbs).

The present study may help to resolve the linguistic dispute about the nature of a verb's argument structure as being syntactic or semantic. A semantic aspect of the verb is stored in the left temporal lobe. But processing of this aspect within a grammatical context is distinctly performed at the left inferior frontal gyrus.

ACKNOWLEDGEMENTS

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Neuromagnetic sensitivity to anomalous vowel nasalization in English

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ABSTRACT

PURPOSE Vowel nasalization was manipulated contrary to the sound combination patterns of English to investigate how auditory processing is affected by a language-specific acoustic anomaly. **METHODS** Six adult native English speakers underwent 151-channel whole cortex MEG during passive auditory presentation of $V_1C_1V_2$ stimuli. In anomalous stimuli, V_1 and C_1 contrasted in nasalization; in control stimuli, V_1 and C_1 matched in nasalization. Averaged MEG epochs for control stimuli were subtracted from corresponding anomalous stimuli to reveal neuromagnetic activity related to encountering a consonant mismatched in nasalization with the preceding vowel. **RESULTS** Anomalous stimuli with nasal V_1 /non-nasal C_1 elicited a neural response component following consonant onset. At the latency of this peak, amplitude was significantly diminished in the anomalous stimulus response. Further, evoked response latency for a non-nasal C_1 was significantly delayed after a mismatched nasal V_1 . **CONCLUSIONS** Results provide neuromagnetic evidence of sensitivity to native language phonology in speech processing. Since nasal vowels are not distinct phonemes in English, the auditory processing system treats vowel nasalization as an acoustic cue for an upcoming nasal consonant; violation of this prediction represents an acoustic anomaly that evokes a specific neural response. Such stimuli would not be anomalous if nasal vowels were not limited to contexts preceding nasal consonants, i.e. if nasal vowels were phonemes in English. This study represents a candidate passive probe for underlyingly intact phonological knowledge in language-impaired clinical populations for whom task-compliance in traditional experimental paradigms is compromised.

KEY WORDS

magnetoencephalography; language; speech perception; auditory processing

INTRODUCTION

This study was designed as an entirely passive MEG paradigm for ultimate use in the investigation of underlying linguistic capacities in language-impaired subjects whose specific deficits are difficult to determine due to unreliable task-compliance using conventional experimental paradigms that require sustained attention and/or repeated responses. The goal was to tap an aspect of auditory speech processing that should be influenced by the native language, incrementally more complex than well-studied categorical perception effects (e.g. Näätänen et al., 1997) but less complex than syntactic/semantic computation. Stimuli were constructed to manipulate vowel nasalization, an acoustic consequence of airflow through the nasal cavity during vowel production that depends on linguistic context in certain languages. In English, nasal vowels arise from anticipatory velum lowering for articulation of a following nasal consonant, unlike languages with nasal vowel phonemes in which their distribution is not limited to contexts before nasal consonants. Since nasalization is predictable from context in English, nasal vowels set up an expectation for a following nasal consonant and oral vowels for a following oral consonant. Stimuli containing violations of these expectations induce processing consequences for English speakers, even though the (within-category) distinction between nasal and oral vowels is not perceptually salient; splicing nasal vowels before oral consonants and vice versa, contrary to the sound patterns of English, yielded reaction time prolongation for consonant identification in a behavioral experiment [Fowler & Brown, 2000]. Similarly anomalous stimuli were constructed here with nasal vowels before oral consonants and oral vowels before nasal consonants, contexts where the vowels would not typically occur in natural production under idealized coarticulatory conditions. We hypothesized that the neuromagnetic activity evoked by passive auditory presentation of these stimuli would reveal selective sensitivity to consonants with unexpected nasalization status based on the preceding vowel, compared to control stimuli in which the consonant and preceding vowel matched in nasalization. This allowed for a straightforward passive experimental design using stimuli with well controlled acoustic properties that can nonetheless be expected to engage knowledge of the sound patterns of the native language acquired during development of subjects' internalized phonological system.

METHODS

Six adult native English speakers (3 female; 2 left-handed; mean age 34 years, range 22-53) gave informed consent to participate. Volunteers were not reimbursed. Subjects lay supine watching soundless videos during MEG recording, instructed only to remain motionless.

Eight VCV stimuli were made from digitized recordings of naturally produced nonsense disyllables [aba]/[āma] (bilabial oral/nasal consonants) and [ada]/[āna] (alveolar oral/nasal consonants). 150ms of the steady state initial vowel was selected from each, along with 350ms of the consonant-vowel sequence, starting with ~100ms of the consonant closure (total duration 500ms, 10ms rise/fall). V_1 from [aba] was combined with C_1V_2 from [āma] to create the anomalous oral V-nasal C sequence [ama]. V_1 from [āma] was combined with C_1V_2 from [aba] to create the anomalous nasal V-oral C sequence [āba]. V_1 from [aba] was recombined with C_1V_2 from [aba] to create the oral V-oral C control stimulus, and likewise for the portions of [āma]; control stimuli thus also contained a juncture point. Junctures were smoothed using a digital sound editor (SoundForge 6.0; Sonic Foundry, Inc., Madison WI USA) to remove clicks. The alveolar stimuli were created identically.

105 trials of each stimulus (ISI 900-1100ms) were randomly presented to subjects' right ear over ER3A (Etymotic Research, Inc., Elk Grove Village IL USA) transducers and ear inserts at 50db SL. MEG epochs of 1200ms were recorded for each trial time-locked to stimulus onset (200ms pre-trigger; SR 1250Hz) in a 151-sensor whole cortex array (CTF Systems, Inc., Port Coquitlam BC Canada) during two 12-minute sessions (i.e. bilabial and alveolar stimuli). MEG data were initially high pass filtered at 1.5Hz; trials containing artifacts with activity over 3 pT were rejected. Epochs were then averaged according to stimulus type and low pass filtered at 40Hz.

The averaged evoked response to each stimulus was examined for each subject to identify the 50 and 100ms automatic sensory responses (i.e. M50 and M100) to onset of V_1 , C_1 and V_2 using left hemisphere sensors (due to monaural right ear presentation). A subtraction analysis was performed on the averaged trials to reveal distinct neuromagnetic activity evoked by the anomalous stimuli. For example, control [aba] was subtracted from anomalous [āba] to hold constant the sensory response to the common [ba] portion of the stimuli; residual activity in the time window following onset of the consonant was inspected for components related to encountering an oral consonant (i.e. /b/) when the initial nasalized vowel induces an expectation for a nasal consonant (i.e. /m/) instead. Likewise, control [āma] was subtracted from anomalous [ama] to hold the

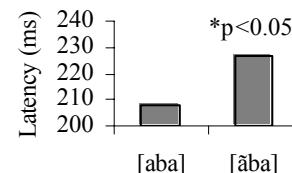
response to [ma] constant; residual activity was inspected for components related to encountering a nasal consonant (i.e. /m/) when the initial oral vowel induces an expectation for an oral consonant (i.e. /b/). Analogous subtractions [ada]-[āda] and [āna]-[ana] were performed for alveolar stimuli. Control [aba]-[āma] and [ada]-[āna] subtractions were performed to ensure that inherent stimulus differences related to the nasalization status of V₁ did not persist into the post-consonant onset portion of the recorded activity.

RESULTS

Results from one subject for whom no evoked components could be identified due to low signal-to-noise ratio could not be included. In another subject, only one session (bilabial stimuli) was completed. Therefore, only 18 of 24 planned subtractions were performed; 9/10 yielded an identifiable peak in anomalous bilabial stimuli and 6/8 in anomalous alveolar stimuli in the 250-400ms post-stimulus onset window (100-250ms after consonant onset). Control subtractions for stimuli in which vowel nasalization matched the consonant yielded no similar peaks. Residual peak activity from anomalous stimuli showed a characteristic magnetic field centered over left auditory cortex with an anterior outgoing field and a posterior ingoing field. Peaks with a latency corresponding to either the M50 or M100 identified for C₁ or V₂ were not counted. No significant latency or amplitude difference emerged between subtraction peaks (anomalous nasal V-oral C 328.1±45.7ms, 26.9±6.7fT; anomalous oral V-nasal C 321.3±38.5ms, 27.7±5.7fT).

However, we measured the amplitude of the r.m.s. of neuromagnetic activity at the latency of each peak identified in the subtractions. In the anomalous nasal V-oral C epochs, amplitude was significantly decreased (15.03±0.85fT, $p<0.05$) compared to the amplitude of the residual peak in all other conditions (oral V-nasal C 20.42±.85fT; nasal V-nasal C 20.89±.75fT; oral V-oral C 20.39±.52fT). This effect was primarily contributed by the bilabial [āba] stimuli.

The averaged waveforms from [āba] revealed that the evoked response to [b] peaked significantly later after a mismatched nasal vowel (226.9±8.8ms) than a matched oral vowel (208.1±6.7ms, $p<0.05$; Fig.1). No other comparison showed a significant difference in the latency of the consonant response.



DISCUSSION

Subtraction peaks demonstrated neuromagnetic sensitivity to acoustic violations of English vowel nasalization patterns in speech sound combinations. The temporal resolution afforded by MEG revealed a significant latency difference of less than 30ms in the evoked response to the consonant in anomalous [āba], a stimulus of the nasal V-oral C type that yielded the amplitude decrease effect. Anomalous oral V-nasal C stimuli showed neither an amplitude effect nor a latency delay in the evoked response to the mismatched consonant. The selective neural response to an unexpected oral consonant after a nasal vowel suggests that nasal vowels induce a stronger prediction for an upcoming nasal consonant than oral vowels do for an upcoming oral consonant for English speakers. This is consistent with reported response asymmetries between speakers of English and Bengali, a language with phonemic vowel nasalization, in a gating task; the former group, but not the latter, took nasalized vowels to indicate a following nasal consonant (Lahiri & Marslen-Wilson, 1991).

Results demonstrate a passive MEG measure of sensitivity to native-language sound patterns in only five normal adult speakers. This study provides a candidate probe for intact language-specific processing in subjects from English-speaking backgrounds with language performance impairments that interfere with assessment of underlying linguistic competence. It is difficult to determine whether language impairment stems from dysfunctions affecting auditory speech processing or fundamental cognitive deficits specific to linguistic representations in children with otherwise normal hearing and intelligence who exhibit developmental language delay. Teasing these possibilities apart can be even more difficult for language-impaired populations such as autistic children, since conventional behavioral and neural language processing experimental paradigms typically require overt task responses that they may not be able to understand or perform consistently. This experiment reveals specific neural activity that reflects how normal auditory speech processing is affected by intact native language phonological knowledge using an entirely passive paradigm. Should the same results emerge in language-impaired children, evidence would be provided for preserved auditory speech processing capacities supported by underlyingly intact native language knowledge, suggesting that the impairments owe to cognitive or processing deficits at a level separate from speech processing deficits or failure to acquire normal representations of the native language phonological system. It has already been demonstrated that children as young as 3 years show neural sensitivity to the difference between nasal and non-nasal vowels in a language without phonemic nasal vowels; deviant nasal vowels in a stream of standard oral counterparts elicited a mismatch response in an MEG oddball paradigm, though with lower amplitude and peak latency than an oddball that crossed a vowel category boundary [Čeponienė et al., 2003]. Taken together with our adult results, anomalous vowel nasalization has the potential to reveal a level of intact language processing in language-impaired children using the bilabial stimuli developed here in a 12-minute (or less, depending on ISI) passive auditory MEG session.

ACKNOWLEDGEMENTS

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Effect of Word Familiarity on Visually Evoked Magnetic Fields

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ABSTRACT

This study investigated the effect of word familiarity of visual stimuli on the word recognizing function of human brain. Word familiarity is an index of the relative ease of word perception, and is characterized by facilitation and accuracy on word recognition. We studied the effect of word familiarity, using "Hiragana" (phonetic characters in Japanese orthography) characters as visual stimuli, on the elicitation of visually evoked magnetic fields with a word-naming task. The words were selected from a database of lexical properties of Japanese. The four "Hiragana" characters used were grouped and presented in 4 classes of degree of familiarity. The three components were observed in averaged waveforms of the root mean square (RMS) value on latencies at about 100ms, 150ms and 220ms. The RMS value of the 220ms component showed a significant positive correlation ($F=(3/36)$; 5.501 ; $p=0.035$) with the value of familiarity. ECDs of the 220ms component were observed in the intraparietal sulcus (IPS). Increments in the RMS value of the 220ms component, which might reflect ideographical word recognition, retrieving "as a whole" were enhanced with increments of the value of familiarity. The interaction of characters, which increased with the value of familiarity, might function "as a large symbol"; and enhance a "pop-out" function with an escaping character inhibiting other characters and enhancing the segmentation of the character (as a figure) from the ground.

KEY WORDS

Language, Familiarity, VEF, MEG, RMS, IPS, Pop-Out

INTRODUCTION

This study investigated the effect of the word familiarity of visual stimuli on the word recognizing function of human brain. Word familiarity is an index of the relative ease of word perception [1], which is determined by subjective ratings with a mental lexicon, and may reflect exposure to words from language production, as well as experiences with auditory, visual, and written forms. Word familiarity is characterized by facilitation and accuracy on word recognition [2], naming times become shorter [1], and the scores of word intelligibilities become higher [2] for high familiarity words than for low familiarity ones.

We studied the effect of word familiarity, using "Hiragana" characters (phonetic characters in Japanese orthography) as the visual stimuli, on the elicitation of visually evoked magnetic fields (VEF) with a word-naming task. The words were selected from a database of lexical properties of Japanese [3], based on auditory familiarity. Visual familiarity of the database was determined with "Kanji" characters (based on Chinese ideograms).

"Hiragana" characters were chosen for visual stimuli to detect the effect of familiarity on the word recognizing function of human brain for two reasons. The first is that "Hiragana" have a one-to-one relationship to pronunciation. In contrast, most "Kanji" characters have multiple pronunciations, and this multiple relationship provokes a lower correlation coefficient between visual familiarity and auditory familiarity [2]. Thus, the correlation coefficient between auditory and visual familiarity rating for words consisting only of "Hiragana" is much higher than the rating for words consisting only of "Kanji" [2]. The correlation coefficient between auditory and visual familiarity was high for "Hiragana" characters even in low familiarity words. The second is that some words with "Kanji" characters of low familiarity are difficult for many people to pronounce, and the words that are difficult to pronounce are not possible to use in naming tasks. "Hiragana" is easier to pronounce and to recognize than "Kanji" for subjects in a lower range of familiarity. The employment of low familiarity words was necessary to observe the effect of a wide range of familiarity. The effect of word familiarity of visual stimuli with "Hiragana" characters was examined from the elicitation of VEF with a word-naming task.

METHODS

Thirteen subjects (10 males and 3 females; mean age ($\pm$ s.d.) 33.7 ± 8.65 years) with normal sight with or without glasses, and without neurological disorders participated in the experiment. All subjects were right-handed.

The four "Hiragana" words, selected from a database of lexical properties of Japanese [3] in lists for word intelligibility [4] based on auditory familiarity, were presented on visual stimuli. The four "Hiragana" words used were grouped and presented in four classes of degree of familiarity, as 7.0-5.5, 5.5-4.0, 4.0-2.5 and 2.5-1.0. Subjects received 400 visual word presentations and were required to name the presented word in a quiet voice as quickly as possible. The voice of the subject was channeled outside of the magnetic shielded room through a 7.5 cm diameter plastic pipe and recorded. In a stimulus train, 100 words in each condition of 4 classes of familiarity were randomly presented on the screen in front of the subject. Each stimulus was of 1000 msec duration controlled by a Ferroelectric Liquid Crystal Light Valve and FLC Driver (DISPLAYTECH, Inc.). ISI was 3000 msec on average, and varied randomly between 2500 and 3500 msec. Visual word presentations were controlled with a stimulus generating program (PsyScope), on a personal computer (Macintosh, Power Mac G3). The words of the 4 "Hiragana" characters were presented on a screen located 164 cm in front of the subject. The images of the words were presented in white characters on a black background at visual angles of 1.7 vertically and 7.0 horizontally, using a liquid crystal projector (IMPRESSION A6+, ASK). Luminance of the characters on average was 37.01 ± 15.14 cd/cm. A 122-channel whole-head detector system (Neuromag Inc., Finland) was used to measure the neuromagnetic responses. The relative position of the subject's head to that of

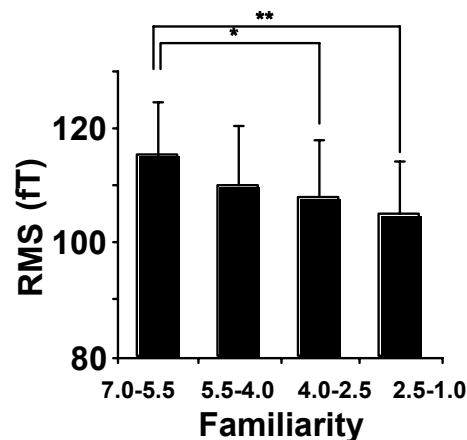


Fig. 1: The root mean square (RMS) value of the third component of 220 ms latency of averaged wave forms of the visually evoked field (VEF) of visual stimuli of four "Hiragana" characters in 4 classes of degrees of familiarities, as 7.0-5.5, 5.5-4.0, 4.0-2.5 and 2.5-1.0. Each point is the mean with SD of 13 normal adults.

the MEG sensors was determined using coils, these positions were determined with three landmark points (the nasion and both the preauricular points) identical to those used in MRI. Throughout the experimental session subjects maintained their vision on a fixation point located in the middle point of the second and third characters, and sat on a chair in a magnetically shielded room. They were instructed to relax and as far as possible not to move or to blink. Neuromagnetic responses were sampled continuously at 400 Hz (0.03--100Hz analog bandwidth). Trigger signals defined the onset of the visual stimulus of the word presentation. MEGs of 100 responses were averaged for 1500 ms, beginning 500 ms before stimulus onset, and corrected for a zero base-line from -200 ms to 0 ms. Off-line digital bandpass filtering reduced the frequency range to 0.5--30

Hz. The equivalent current dipoles (ECDs) of the 220ms component were calculated with a single -dipole algorithm using the magnetic signals at 18 channels, which included a pair of positive and negative peaks. ECDs were judged by criteria: the goodness-of fit (GOF) was above 80% for the peak of the 220ms component, the 95 % confidence volume was less than 4.2 cm³, and the volume included gray matter. Three-dimensional T1-weighted MRI scans were obtained for all subjects using a 0.3 Tesla MRI System (AIRIS II, HITACH, JAPAN). Averaged wave forms of the visually evoked fields (VEFs) were obtained in the four familiarity conditions in all subjects. The root mean square (RMS) value was determined with all MEG channels. The amplitude of the RMS value of the VEF was examined for the 4 degrees of the word familiarities.

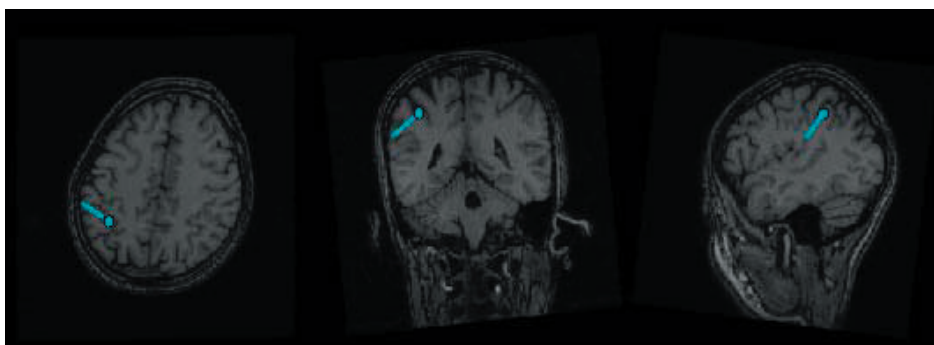


Fig. 2: ECDs of the 220ms component are superimposed on an anatomical image of one subject. For the ECDs, the solid circle denotes localization and the line denotes orientation of the moment. ECDs of the 220ms component are localized in the IPS area.

RESULTS

The three components were observed in the averaged waveforms of the RMS values on latencies of about 100ms, 150ms and 220ms. The RMS value of the 220ms component showed a significant positive correlation ($F=(3/36)$; 5.501; $p=0.035$) with the value of familiarity. Significant increments of the RMS were observed in the degree of familiarity between 7.0-5.5 and 2.5-1.0 ($p=0.004$, +9.5%), 7.0-5.5 and 4.0-2.5 ($p=0.0134$, +6.5%). ECDs of the 220ms component were observed in the intraparietal sulcus (IPS) (Fig. 2). ECDs for the IPS were detected in the left (6/13 cases) and right (3/13 cases) hemispheres.

DISCUSSION

ECDs of the 220ms component were observed in the IPS areas. The IPS is responsible for lexical agraphia, difficulties in writing irregularly spelled words, and easiness of writing words that have rules of phoneme-to-grapheme translation [5]. Patients with lexical agraphia have lesions that overlap in the region of the IPS. Ideographic characters as well as irregularly spelled words may be retrieved "as a whole" within the system in the IPS, which has a function as the global identification system of the whole character/word form [5]. Increments in the RMS values of the 220ms component, which might reflect ideographical word recognition retrieving "as a whole", were enhanced with increments of the values of familiarity.

The parietal areas including the IPS were activated with the efficient pop-out condition during the visual search using functional magnetic resonance [6]. Increments in the RMS value of the 220ms component might reflect a "pop-out" function on visual stimuli of the 4 "Hiragana" characters. The interaction of characters, which increased with the value of familiarity, might function "as a large symbol"; and enhance the "pop-out" function with an escaping character inhibiting other characters and enhancing the segmentation of the character (as a figure) from the ground.

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Cortical oscillations modulated by congruent and incongruent audiovisual stimuli

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ABSTRACT

Congruent or incongruent grapheme-phoneme stimuli are easily perceived as one or two linguistic objects. The main objective of this study was to investigate the changes in cortical oscillations that reflect the processing of congruent and incongruent audiovisual stimuli. Graphemes were Japanese Hiragana characters for four different vowels (/a:/, /ou/, /u:/, and /i:/). They were presented simultaneously with their corresponding phonemes (congruent) or non-corresponding phonemes (incongruent) to native-speaking Japanese participants. Participants' reaction times to the congruent audiovisual stimuli were significantly faster by 57ms as compared to reaction times to incongruent stimuli. We recorded the brain responses for each condition using a whole-head magnetoencephalograph (MEG). A novel approach to analysing MEG data, called synthetic aperture magnetometry (SAM), was used to identify event-related changes in cortical oscillations involved in audiovisual processing. The SAM contrast between congruent and incongruent responses revealed greater event-related desynchronization (8-16 Hz) bilaterally in the occipital lobes and greater event-related synchronization (4-8 Hz) in the left transverse temporal gyrus. Results from this study further support the concept of interactions between the auditory and visual sensory cortices in multi-sensory processing of audiovisual objects.

KEY WORDS: magnetoencephalography, audiovisual, phoneme, grapheme, congruent, event-related synchronization

INTRODUCTION

Cross-modal sensory binding is necessary for learning to read a written language. Phonemes (auditory events) must be properly associated with their corresponding graphemes (visual events). After such associations have been learned, congruent grapheme-phoneme stimuli are perceived as one perceptual object whereas as stimuli that do not match are perceived as incongruent objects. Functional neuroimaging techniques, such as magnetoencephalography (MEG), might show the timing and location of the neural activity that processes this difference. Raji et al. [Raji, 2000] identified greater MEG activation in the middle part of the left superior temporal sulcus (STS) for congruent than incongruent stimuli. This suggests that the left STS is involved in cross-modal sensory integration and that there is an enhancement when grapheme-phoneme stimuli are congruent. Other studies using MEG and fMRI have reported similar findings in the STS and auditory cortex for speech (i.e. lip-reading + vocalized sound) stimuli [Calvert, 2001]. However, these changes in the time signal of the evoked MEG fields and in blood flow only reflect part of the changes in cortical activity to audiovisual stimuli. Ongoing cortical oscillations are also modified by a stimulus event. The most widely known modulation of cortical oscillations is the event-related synchronization (ERS) and desynchronization (ERD) of the posterior alpha rhythm (8-16Hz) when subjects close and open their eyes, respectively. Smaller event-related changes in ongoing cortical rhythms may also be elicited by changes in auditory and visual stimuli [Pfurtscheller, 1999]. The intent of this study was thus to investigate the event-related changes of cortical oscillations that reflect processing differences between congruent and incongruent grapheme-phoneme stimuli.

METHODS

PARTICIPANTS: Thirteen native-Japanese participants (seven females) with normal audiological and neurological status volunteered for this study. All participants' first written and spoken language was Japanese. Participants were between the ages of 21 to 38 years (mean age 29 years) and all were right-handed.

STIMULI: Audiovisual stimuli were phonemes and Hiragana graphemes for the vowels: /a:/, /ou/, /u:/, and /i:/ (Figure 1). Phonemes were presented binaurally at 60 dB SL (sensation level). Graphemes were presented as white symbols on a black background and covered 4° of the central visual field. Two equiprobable categories of audiovisual stimuli occurred randomly: 1) congruent – the phoneme sound matched the grapheme, and 2) incongruent – the phoneme sound did not match the grapheme.

BEHAVIOURAL MEASUREMENT: These measurements were taken in a separate block from the MEG recordings. One hundred audiovisual stimuli were randomly presented for a duration of 600 ms; immediately followed by a cross hair at a central fixation point on the screen. The participant's task was to categorize the congruent and incongruent stimuli by pressing one of two buttons with their left index or middle finger as fast and as accurately as possible. After the participant's button press, there was a 1 sec delay before the presentation of the next stimulus. Participants' reaction times and accuracies were recorded.

MEG MEASUREMENT: Four hundred audiovisual stimuli were randomly presented for a duration of 600 ms. A 300 ms black screen followed each audiovisual stimulus and then a cross hair appeared at central fixation point for a random duration of 2000-2500 ms. The participant's task was to press one of two buttons, depending on stimulus category, using their left index or middle finger. In order to decrease any MEG effects of motor activity on the responses to the audiovisual stimuli, the participants were asked to withhold their response until the cross hair appeared

MEG ACQUISITION: Cerebral magnetic fields were recorded in a magnetically shielded room using a 151-channel whole-head biomagnetometer system (CTF Systems Inc.). Stimulus-related epochs of 3 sec duration that included a 1 sec pre-stimulus baseline were recorded at a sampling rate of 625 Hz. Epochs were band-pass filtered from DC to 104 Hz for online recording. The head position was checked before and after the recording session. The data for three subjects were not analyzed because of head movements greater than 10 mm.

MEG DATA ANALYSIS: SAM is an analysis technique that is based on the concept of using non-linear beamformers to spatially filter the data from unwanted interference source activity [Robinson, 1998]. SAM methods used in the present study are similar to those previously described in detail by Herdman et al. [Herdman, 2003]. To summarize these methods, SAM volumetric maps are produced by calculating the power differences, within a selected frequency band, between an active and control window for each voxel in the brain. These power differences are represented as positive and negative pseudo t-values, which reflect event-related synchronizations and desynchronizations, respectively. For both congruent and

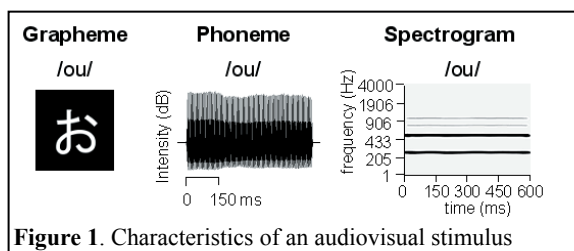


Figure 1. Characteristics of an audiovisual stimulus

incongruent stimuli, SAM maps were calculated in the frequency bands of 4-8Hz and 8-16Hz for contrasts between 0-250ms pre-stimulus (i.e. baseline) and 0-250ms post-stimulus onset, as well as 250-500ms post-stimulus onset. Additionally, SAM maps were calculated in the frequency bands of 4-8Hz and 8-16Hz for contrasts between congruent and incongruent post-stimulus activity in the time windows of 0-250ms and 250-500ms. Statistically significant group SAM volumetric maps were obtained by permutation analysis (see Herdman et al., 2003).

RESULTS

BEHAVIOURAL RESULTS: Participants' reaction times for congruent and incongruent grapheme-phoneme stimuli were 601 ± 157 ms and 658 ± 185 ms, respectively. Results from a Student's t-test revealed that reaction times for congruent stimuli were significantly shorter than to incongruent stimuli ($p < 0.006$). There was no significant difference in response accuracies between congruent and incongruent stimuli ($96 \pm 3\%$ and $98 \pm 4\%$, respectively).

MEG RESULTS: Significant voxels ($p < 0.025$ by permutation testing) for event-related cortical activity to congruent and incongruent stimuli are overlaid on axial slices of a normalized structural MRI (Figure 2). For the 4-8Hz frequency band in the early time window (0-250ms), significant voxels only had positive pseudo t-values and revealed an ERS occurring left superior temporal gyrus (Figure 2A, upper and middle panels). This left temporal region encompasses Heschl's gyrus and the planum temporale. The contrast between responses to congruent and incongruent stimuli for the 4-8Hz band revealed greater ERS in the left transverse temporal gyrus for congruent audiovisual stimuli (Figure 2A, lower panel). For the 8-16Hz frequency band in the late time window (250-500ms), significant voxels only had negative pseudo t-values and reveal an ERD occurring bilaterally in the middle and superior occipital gyri (Figure 2B, upper and middle panels). The contrast between responses to congruent and incongruent stimuli within the 8-16Hz band revealed greater ERDs in bilateral occipital cortices for congruent audiovisual stimuli (Figure 2B, lower panel).

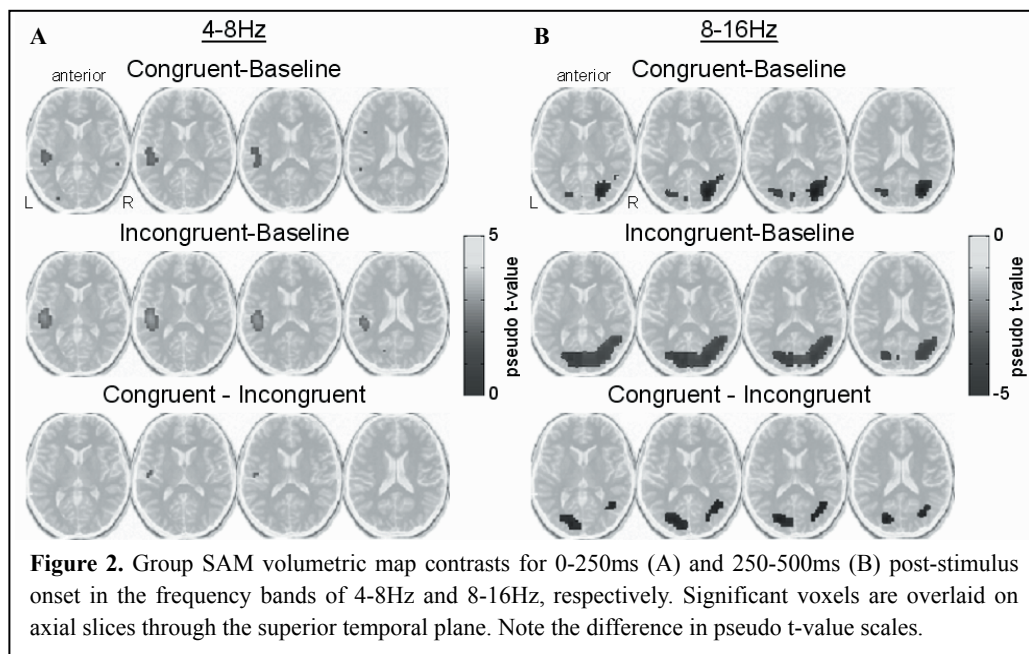


Figure 2. Group SAM volumetric map contrasts for 0-250ms (A) and 250-500ms (B) post-stimulus onset in the frequency bands of 4-8Hz and 8-16Hz, respectively. Significant voxels are overlaid on axial slices through the superior temporal plane. Note the difference in pseudo t-value scales.

DISCUSSION

Results from the present study indicate cortical processing (i.e., ERS and ERD) in auditory and visual sensory cortices for both congruent and incongruent grapheme-phoneme stimuli. These cortical events are enhanced in the left auditory cortex and in bilateral occipital cortices for congruent grapheme-phoneme stimuli. Enhanced ERS in the 4-8Hz frequency band is similarly located in the left auditory cortex to the enhanced evoked response reported by Raij et al. [Raij, 2000], except that it occurred within 0-250ms as compared to 380-540ms. These results suggest that early changes (0-250ms) in induced neural oscillations lead to later changes (380-540ms) in the phase-locked (evoked) activity. We additionally found that there is enhanced visual processing for congruent stimuli as reflected by the increased ERDs for the 8-16Hz frequency band. These enhanced regions of cortical activity suggest an increased interplay between the auditory and visual cortices during the processing of the congruent stimuli. This could cause the reaction times to be 57 ms faster to congruent than incongruent grapheme-phoneme stimuli.

ACKNOWLEDGEMENTS

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Multi-Language Area Activities in Sentence Reading

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ABSTRACT

In order to identify neural correlates that underlie syntax processing in language, phrase-to-phrase analysis of neural responses while subjects are reading a whole sentence would be desirable. Here, we performed a MEG study using Japanese complex sentences with an embedded clause, which were visually presented phrase by phrase. The largest response peaks appeared in 150-300 ms, which represented the neural activities in the occipito-temporal regions along the ventral pathway. In addition to these, we observed later responses in 300-600 ms, which had concurrent activities in different cortical regions including the prefrontal, inferior temporal and superior temporal to inferior parietal areas. Such activities were concentrated in those areas for the sentences that had a moved phrase, i.e., an important syntactic operation, as compared with the sentences in normal phrase order. The present observations suggest that multiple language areas contribute to syntax processing in sentence comprehension.

KEY WORDS

MEG, language, sentence comprehension, syntax

INTRODUCTION

In recent neuroimaging studies using PET and fMRI, controversies exist as to the brain regions that support syntactic processing of sentences. Studies using comprehension/grammatical judgment tasks of sentences have suggested Broca's area (Brodmann's areas 44/45) in the inferior frontal cortex as the main syntactic center or the center specifically involved in syntactic processes [Dapretto, 1999][Emblück, 2000]. However, studies using the sentences with syntactic difficulty and violation have suggested that different cortical regions, other than Broca's area, including the superior temporal cortex (Wernicke's area) are activated, where the activation of Broca's area is thought to be associated with the demands on memory and computation that the task imposes [Just, 1996][Caplan, 1998][Keller, 2001]. Since syntax is deeply related to the analysis of sentence structure, phrase-to-phrase detection of neural responses while subjects are reading a whole sentence that has syntactically specific structure would be desirable. Here, we performed a MEG study using Japanese complex sentences, visually presented phrase-by-phrase, having a movement of phrase within sentence, which is an important syntactic operation in human language. We aimed to find cortical activities across phrases, analyzing MEG responses from the first noun phrase to the ending verb phrase of the sentence.

METHODS

We used Japanese complex sentences with an embedded clause structure. Japanese is a S(subject) - O(bject) - V(verb) language in which word order is relatively free except for the fact that the verb must appear in sentence-final position. The complex sentences used in this experiment had a form of NP(S)+[NP(S)+NP(O)+VP(V)]_C+VP(V), where embedded complement clause is indicated by []_C, and NP and VP stand for the noun and verb phrase. An example sentence, which is translated phrase to phrase in English, in the above form is:

↑ “The boys (S) [that the friends (S) their teacher (O) visited (V)] said (V).” (The boys said that the friends visited their teacher.)

In addition to such canonical (CAN) sentences in normal phrase order, we also used scrambled sentences (SCR) in which the object phrase NP(O) is moved to the sentence top, as indicated by an arrow. Such phrase-movement, without changing the meaning, is allowed in Japanese syntax.

A total of 120 canonical and 120 scrambled sentences were prepared. These sentences were presented visually phrase-by-phrase in a pseudo-randomized order. In a previous pilot study [Kuriki, 2002] a long inter-stimulus-interval (ISI) of 1200 ms was set between the third NP and its subsequent VPs to observe the NP and VP responses separately. However, MEG responses to the VPs were attenuated in amplitude due to the long intermission, which might have reduced the subjects' attention to the last VPs. In this experiment, all the phrases were presented at a same rate of 400 ms ON and 400-550 ms OFF. This corresponds to a rate of about 4.5 characters/s, which is half of normal reading speed of Japanese sentence.

Subjects performed a thematic-role assignment task during MEG recording, answering yes or no by key-press to a question that appeared 900 ms after the final phrase of each sentence. The question was given in a short descriptive sentence of “Who did whom what?”, relevant to the theme of the embedded clause. It is noted that due to the verb-final characteristic of Japanese, the thematic role can not be assigned, or understood, until the final verb of the sentence is encountered. Three right-handed male subjects (aged 23-27 years old) participated in the experiment.

MEG responses during a period of whole sentence were recorded with a whole-head SQUID magnetometer (Neuromag, Helsinki). Responses of correct answers were recorded and averaged for each of three NPs and two VPs, being separated into CAN and SCR sentences. The averaged responses were filtered digitally to 0.3-30 Hz, where a 300 ms prestimulus period in which the response to a previous phrase ceased served as the baseline. Distributed current densities, i.e., equivalent current dipoles (ECD) per volume, were estimated as the sources of response components. The source space was constrained on the lattice points within the cortex including sulci, where about 5000 points were assigned in individual MR images. Minimum L1-norm reconstruction in a software package (Neuroscan, El Paso) was used to calculate the distribution of dipole sources. Here, L1-norm method gives the solution with minimum number of dipoles, which may meet an assumption of regionally concentrated neural activities. A simulation study prior to the data analysis was conducted. Location errors of within 5 mm in three coordinate axes were obtained with rms noise-to-signal ratio of 0.17-0.51, except of 5-15 mm errors in the anterior-posterior axis for the frontal source and lateral-medial axis for the temporal source.

RESULTS

MEG response peaks were observed in all the phrases of sentence (Fig. 1). Large peaks appeared at 150-250 ms, which were ascribed mostly to the ECD sources in the occipital and occipitotemporal regions, representing the neural activities in higher visual cortices [Kuriki, 2002]. We describe hereafter late responses appearing after 300 ms. The first NP response tended to have larger amplitude of late responses than the second and third NPs in both CAN and SCR sentences, while the late responses were not significantly different between the two VPs in CAN and SCR sentences.

Fig. 2 summarizes ECD sources localized by L1-norm reconstruction for three subjects, where ECDs at latencies of 300-600 ms were selected for goodness-of-fit of more than 75% and the moment of more than 5 nAm to represent major activities. Though limited by small number of subjects, the results indicate that different cortical regions that may be associated with language functions are activated. Those regions in the left hemisphere include prefrontal areas, inferior and superior temporal areas, areas from the posterior end of sylvian fissure (supramarginal gyrus) to the angular gyrus, and inferior parietal areas. Compared with CAN sentences, activities in SCR sentences had concentrated sources of NPs in the inferior temporal, posterior-superior temporal and inferior parietal areas. SCR sentences also showed consistent activities of VPs across three subjects, while only single subject showed major activities in CAN sentences. Activities in the right hemisphere were observed mostly in homologous regions to those in the left hemisphere, but the ECD sources were not concentrated to regions and consistent across subjects.

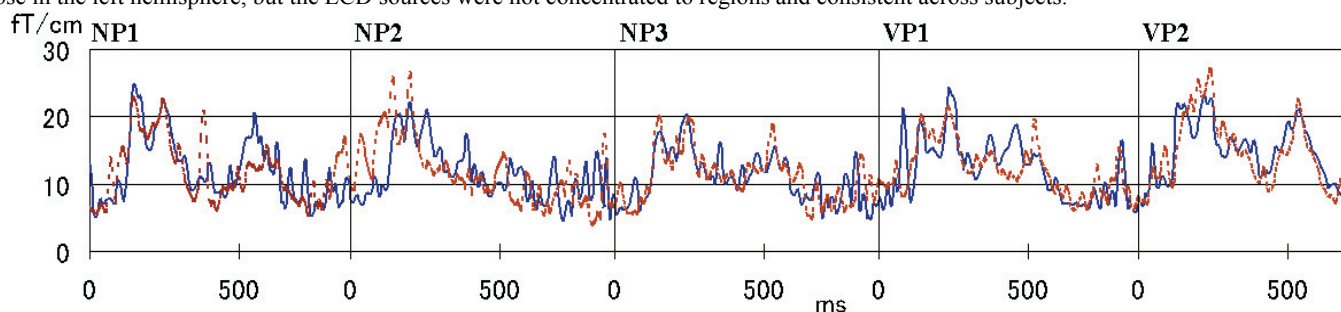


Fig. 1. Waveform of recorded MEG responses in one subject, where root-mean-squared (RMS) amplitude over left-hemisphere channels is shown for successive phrases of canonical (solid line) and scramble (broken line) sentences.

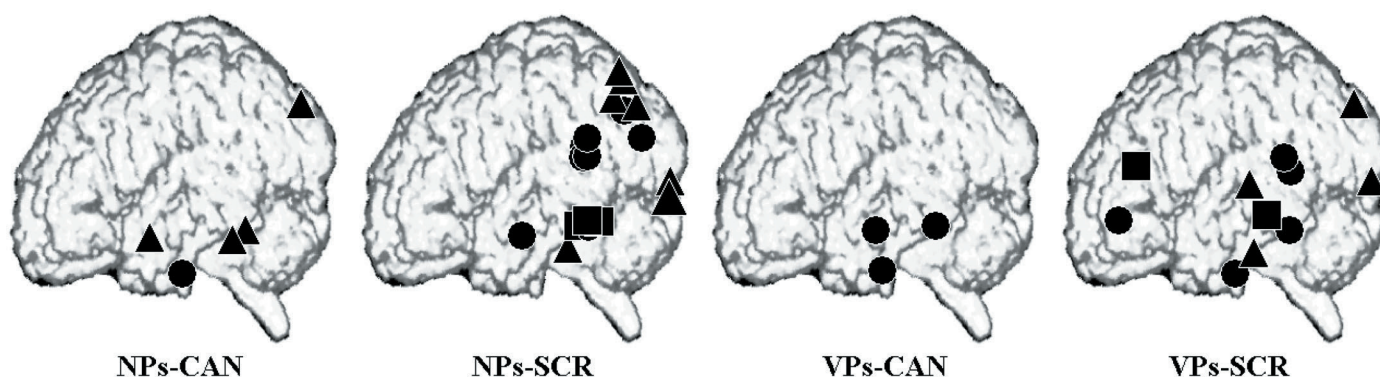


Fig. 2. ECD sources localized for late responses of more than 300 ms. The results in three subjects, indicated by different symbols, for canonical (CAN) and scrambled (SCR) sentences are summarized across three noun phrases (NPs) and two verb phrases (VPs).

DISCUSSION

In contrast to our previous results [Kuriki, 2002], clear late responses after 300 ms were observed not only for NPs but also clause-ending VPs, indicating that continuous presentation of phrases at a constant rate is crucial for reliable observation of endogenous components. The effect of scrambling, i.e., movement of an object noun phrase to the sentence-top position, is reflected in the largest response amplitude of the first NP among the three NPs due to an enhanced attention of subjects. In addition, SCR sentences showed regionally concentrated activities consistently across subjects, as compared with CAN sentences. The observed activities in different cortical areas of the prefrontal, temporal and inferior parietal regions for SCR sentences suggest that wide range of neural network subserves the comprehension of sentence in support of previous fMRI/PET studies [Just, 1996][Keller, 2001]. Enhanced activities in the dorsolateral prefrontal areas and the supramarginal/angular gyri may reflect the increased demands on working memory or phonological encoding.

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Auditory evoked field responses in the left hemisphere to morphosyntactic violation in Korean sentence

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ABSTRACT

To investigate multiple cortical regions associated with syntactic processes at the sentence level, auditory evoked field responses to morphosyntactic violations were measured over the left hemisphere of seven subjects. Subjects were asked to judge the acceptability of the final verb in verb-ending Korean sentence. Measured field data were transformed to the fields that would be detected on a standard sensing plane and averaged across subjects in different violation conditions. In the grand average data, we found distinct features at latencies of 400 ms and 600 ms, which seem to be specific to morphosyntactic processes. ECDs plotted on a standard brain indicate the inferior frontal region and the superior temporal gyrus for 400 ms component, and the middle temporal gyrus for 600 ms component. Our MEG study localized the distinct cortical regions involved in syntactic processes, which may be reflected in LAN and P600 of ERP.

KEY WORDS

Auditory evoked fields, Morphosyntactic, Sentence comprehension, LAN, P600, Grand average

INTRODUCTION

Previous ERP studies revealed the specific temporal components that are correlated with syntactic processes in sentence comprehension and brain imaging studies suggest multiple areas that are not involved uniquely in syntactic tasks [Kaan, 2002]. Recently, several MEG studies specified the temporo-spatial parameters of syntactic processes [Knösche, 1999]. These studies commonly reported the involvement of the inferior frontal cortex and parts of temporal region in syntactic processes, however, it still remains unclear which cortical areas revealed by the imaging studies are responsible for the specific ERP components.

The purpose of the present study is to seek the activated regions that are responsible for the temporal components elicited by syntactic violations in the auditory sentence, while changing the verb in morphosyntactic manners in a verb-ending sentence. As an experimental language, we used Korean, which has a subject-object-verb order (SOV) structure, ending with a verb. The thematic role of nouns, such as nominative (*NOM*), dative (*DAT*), and accusative (*ACC*), is assigned by postpositional particles attached to the nouns as case markers. Thus, in Korean, the thematic role of a noun can be determined without considering the subcategorization information of the used verb and the word order in a sentence is relatively free compared with English. In addition, the properties of verb, such as tense, voice, and sentence type, are defined by adding or deleting the morphological affixes following the verbal stem. In a sentence, there are several 'Eojeol's which are composed of several morphemes or words, being smaller than phrases but larger than words (Figure 1). Eojeols are the main components of meaning. Due to the way of Eojeol composition, Korean is called an agglutinative language.

(a) 아이가 정원에서 나무를 꺾었다

(A child in the garden the branch of a tree broke)
NOM ACC V

(b) 아이가 정원에서 나무를 꺾었다

(A child in the garden the branch of a tree was broken)
NOM ACC V

Figure 1. Examples of Korean sentence in (a) correct, (b) morphosyntactic violation conditions.

METHODS

Seven healthy, all right-handed adults (mean age 29 years, range 24-40 years) participated in this study after giving informed consent. All subjects were males and native speakers of Korean with no known hearing deficit and no history of neurological diseases.

All sentences consist of four Eojeols with verb-ending. The final verb is a three-syllable word, where the first syllable is the verbal stem representing the meaning of the verb and the second syllable represents the tense and the voice. The last one is a descriptive ending. Since all sentences contained a preceding object noun (*ACC*), the final verb should be made active. Morphosyntactic violation was generated by a morphological change of the second syllable of the final verb in the correct sentences, from active to passive voice. A total of 218 sentences, consisting of canonical and violated sentences, pronounced by a female speaker were recorded and were digitized.

The sentences were applied monaurally in a random order to the right ear of each subject and subjects were asked to judge covertly whether the final verb was adequate with respect to the preceding context of the sentence. MEG responses elicited by the verb were measured above the left hemisphere, covering the temporal region and a part of the frontal region and averaged for all epochs. In contrast to the radial component, we measured two orthogonal field components (B_x and B_y) parallel to the bottom of the flat-tip dewar using 40-channel SQUID system and then the magnetic field map of the tangential components has an amplitude peak just above the dipolar source current [Kwon, 2002].

The averaged fields of each subject were transformed into the fields that would be detected on a standard sensing plane, and grand average data were calculated over all subjects [Kwon, 2004]. To do it, distributed ECDs that could explain the measured fields were estimated within a spherical conductor by the conventional weighted minimum norm estimation. The root mean square of the grand average data within 50 ms period in different violation conditions were used for statistical analysis (ANOVA). For showing the distribution of significant effects, paired t tests were calculated for every single sensor location. The mean location of the activated areas over multiple subjects was obtained from the grand average data.

RESULTS

Compared with correct condition, the grand average waveform of the evoked responses to morphosyntactic violation conditions exhibited prominent features of 400 ms and 600 ms components in the time window of 400-450 ms ($F_{1,6}=7.17$, $p=0.037$), 550-600 ms ($F_{1,6}=6.57$, $p=0.043$) and 600-650 ms ($F_{1,6}=11.8$, $p=0.014$). Paired t-tests between the two conditions in the responses at each channel revealed significant differences in the

anterior (400 ms) and inferior central (600 ms) region of recording area. In Figure 2, (a) and (b) show the grand average of the field distribution of 400 and 600 ms components in morphosyntactic violation condition. Here, the grey scale in (a) and (b) was normalized by the maximum field of 50 and 95 fT, respectively, and bright region indicates the maximum. The contour pattern of 400 ms component indicated major activations in two regions within the recording area, i.e., the anterior part where a significant difference was observed in the waveform and the central part. These two activations were localized at (5.2, 5.8, 5.3) cm in the head coordinates with a goodness-of-fit of 86.6 % and (-0.6, 5.6, 4.9) cm with a goodness-of-fit of 88.5 %, respectively. The field pattern of 600 ms component indicated an ECD in the region slightly inferior to the auditory cortex and a posteriorly directed dipole was obtained with a goodness-of-fit of 95.7 % at a site of (-0.8, 5.2, 3.8) cm. Anatomically, these ECDs plotted on a standard brain indicate the left inferior frontal gyrus (IFG, BA 45) and the superior temporal gyrus (STG) for 400 ms component (square) and the middle temporal gyrus (MTG) for 600 ms component (triangle), respectively, as can be seen in Figure 3. Here, circle indicates the source of N100m by 1 kHz tone stimulus.

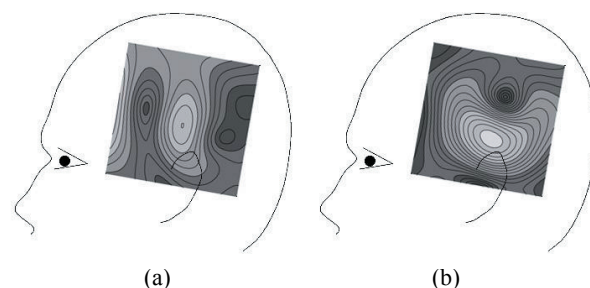


Figure 2. Grand average of the field distribution of (a) 400 ms and (b) 600 ms components in morphosyntactic violation condition.

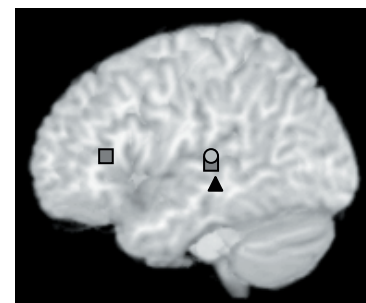


Figure 3. ECD localization results.

DISCUSSION

The purpose of this study is to specify common areas across subjects of the neural activity that is responsible for temporal components in sentence-level syntactic processing. Here, morphosyntactic violation was generated by substituting of an active verb *broke* by passive verb *was broken* in verb-ending sentence and it was realized by a morphological change of the second syllable of the verb whereas the verbal stem is common (Figure 1). In Korean, the thematic role of a noun can be determined without considering the subcategorization information of the used verb. Therefore, normal subjects can detect a mismatch between the passive voice of the verb and the thematic role of the preceding noun (*ACC*) without semantic processing difficulty. In this manner, we observed clear peaks at latencies of 400 and 600 ms in the grand average waveform of the responses to syntactic violation compared to correct condition. The field distribution and ECDs plotted on a standard brain suggest that the left IFG (BA 45) and the left STG are responsible for the 400 ms component and the left MTG for the 600 ms component. Several studies reported activation of BA 45 in syntactic structure when disentangling grammar from semantics [Caplan, 1999] [Moro, 2001]. Interestingly, it was suggested that the functional role of pars triangularis (BA 45) at the left IFG includes thematic analysis involving the verb and its argument [Newman, 2003]. In the temporal domain, previous ERP study reported a LAN-like-P600 pattern for type of argument error (*DAT* instead of *ACC* case marking) [Friederici, 2000]. Therefore, BA 45 and MTG seem to be responsible for a LAN and a P600, respectively, whereas the STG activation of 400 ms component may reflect the semantic aspects included in the morphosyntactic violation [Kwon, 2004]. So far, several regions have been suggested as neural generators of syntactic processes in previous studies, however, there are only a few studies which provide spatial information on a P600, i.e., the anterior medial temporal lobe [Dien, 2003], the posterior portion of STG and the left basal ganglia [Kotz, 2003].

In conclusion, the results of our MEG study suggested distinct cortical regions involved in syntactic processes, which may be reflected in a LAN and a P600 of ERP. The estimated regions are the left IFG (BA 45) for a LAN and the left MTG for a P600. However, our measurements were made over the left hemisphere with limited coverage of sensors. Extending the measurement to the whole cortex would be a subject of further study.

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Head Position in the MEG Helmet Affects the Sensitivity to Anterior Sources

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ABSTRACT

Current MEG instruments derive the whole-head coverage by utilizing a helmet-shaped opening at the bottom of the dewar. These helmets, however, are quite a bit larger than most people's heads so subjects commonly lean against the back wall of the helmet in order to maintain a steady position. In such a case the anterior brain sources may be too distant to be picked up by the sensors reliably. Potential "invisibility" of the frontal and anterior temporal sources may be particularly troublesome for the studies of cognition and language, as they are subserved significantly by these areas. We examined the sensitivity of the distributed anatomically-constrained MEG (aMEG) approach to the head position ("front" vs. "back") secured within a helmet with custom-tailored bite-bars during a lexical decision task. The anterior head position indeed resulted in much greater sensitivity to language-related activity in frontal and anterior temporal locations.

KEY WORDS: MEG, cognition, language, frontal cortex, head position, bite-bar.

INTRODUCTION

The extraordinary capability of MEG to detect very weak magnetic signals relies on the cryogenic methodology. Its sensors are immersed in liquid helium, surrounding the head in the helmet-shaped opening at the bottom of the dewar. In order to accommodate over 95% of the head shapes and sizes, the helmet is quite a bit larger than most people's heads. Magnitude of the dipolar magnetic field decreases with the square of the distance between the source and the sensor [Lewine,1995]. Hence, the sensors located closer to the sources in the brain are more sensitive to the signal than those further away. Because most recordings are performed without imposing any physical constraints on the position of the head inside the dewar, subjects find it necessary to find a spatial "frame of reference" in an effort to comply with the requirements to sit still. Commonly, they recline and lean their heads against the back of the helmet. This makes it less effortful for the subjects to maintain a constant position during the recording. In this case, the posterior regions of the brain will be close to the sensors and will contribute more to the overall signal. In contrast, the frontal sources will be at a disadvantage and their contributions may not be picked up by the sensors at a distance. On the other hand, the dSPM solution (see in Methods) is normalized to the noise estimated to arise from each dipole location. Since most MEG noise is biological, the decreased signal arising from sources at an increased distance from the sensors should be partially compensated by decreased noise assigned to that location. If, however, posterior head positions render MEG insensitive to anterior sources, this would create a serious problem for many cognitive studies where frontal and anterior temporal activity is prominent [Halgren,1994] [Fiez,1998]. Therefore we wished to explore effects of the head position on the "visibility" of the anterior brain sources during a standard language task. The primary aim of our study was to examine the sensitivity of the distributed solutions to the head position ("front" vs. "back") in a standardized helmet-shaped whole-head dewar.

METHODS

Five healthy subjects (4 men, mean age: 23.8) participated in a lexical decision task that required responding to real words with one hand and to pronounceable (e.g. *belez*) and nonpronounceable (e.g. *rtjkzd*) letter strings with the other. The letter-strings (150 per condition) were presented for 278 ms every 2.1 seconds and subtended $<5^\circ$. Response-hands were switched mid-way through each experiment and the order was counterbalanced across subjects. Each subject participated in two successive experiments during the same session whereby the head was positioned towards the front end of the helmet during one run and towards the back of the helmet during the other run. In both cases the subject's head was touching the top of the helmet, so that the main difference in positioning was along the y-axis. The order was counterbalanced across subjects as they performed the same task but with different stimuli during each run. The position of the head in the dewar was determined by digitizing the four magnetic coils that were affixed to the head (behind the ears and just below the hairline on each side of the midline on the top of the scalp) and remained constant for both successive runs. In addition, a series of points across the head surface were digitized with 3Space Isotrak II system for subsequent precise co-registration with MRI images. The two respective head positions were secured with the use of custom-tailored bite-bars. A different bite-bar was made for the "front" and the "back" positions for each subject. In order to create a bite-bar mouthpiece, a plaster cast of the upper teeth was first made. A layer of thermo-forming mouthguard material was molded over the cast and then a layer of rigid baseplate material was molded over the mouthguard inner layer. The mouthpiece was to a U-shaped bar which was firmly affixed to the sides of the dewar (Fig. 1). By fixing the upper jaw, these bite-bars provided head positions for the "front" and "back" runs respectively, while minimizing motion.

MEG signals were recorded from 204 channels (102 pairs of planar gradiometer) with a whole-head Neuromag instrument (4-D Neuroimaging) in a magnetically and electrically shielded room. Artifact-free averages for each stimulus type were constructed on-line. Each person's cortical surface was reconstructed from high-resolution T1-weighted MRI structural images (1.5T Siemens Allegra), and it served as the constraint for the anatomically-constrained MEG (aMEG) solution estimates. Dipole orientation was unconstrained and the forward solution used a boundary element model [Dale, 2000]. Dipole strength power was estimated at each cortical location using a noise-normalized linear minimum norm approach [Dale, 2000] [Hämäläinen, 1994], resulting in "brain movies". Group average dynamic statistical parametric maps (dSPMs) of the estimated activity.

RESULTS

Subjects were indeed able to maintain constant head positions throughout the "front" and "back" runs, as evidenced by an average displacement of 0.25 mm as measured before and after each of the two runs. The coil position displacement between the "front" and the "back" positions was apparent mainly in the y axis (16.1 mm on average), whereas the differences in the coil positions along the x and z axes were comparably small (1.2 and 2.1 mm respectively). Effects of the head position difference on the currents estimated with the aMEG approach are presented below. Figure 2 illustrates the difference detected by the sensors in one subject. Average waveforms to real words recorded in the "front" (black lines) and "back" (gray lines) positions are superimposed. Two gradiometer sensor pairs show larger evoked fields over the left frontal area when the head is positioned towards the front, than when it is in an unrestrained "default" position leaning against the back of the helmet. Figure 3 illustrates the difference in dSPM solutions obtained under two head positions ("front" on the left and "back" on the right) during 400-550 ms latency window. Estimates in the

“back” position primarily include the posterior temporal (Wernicke’s area) and the posterior inferior prefrontal regions. In contrast, the “front” position reveals a more extended pattern of the estimated sources at this latency, particularly in the frontal and anterior temporal regions. In an effort to provide a rather conservative test, four out of five of our subjects were males and some of them had quite large heads. Nevertheless, significant differences in sensitivity to anterior sources emerged as a function of the head position in the helmet.



Fig. 1. Upper-jaw bite-bar mouthpieces were made for each subject and for each head position. They are attached to a bar that is firmly affixed to the sides of the dewar.

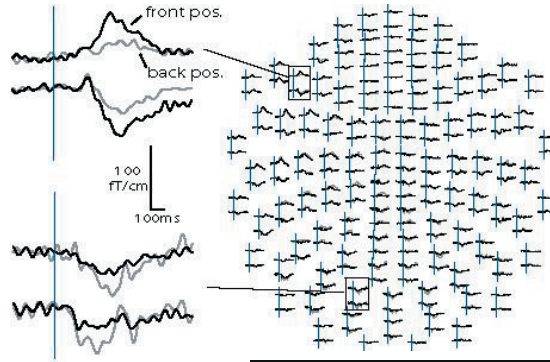


Fig. 2. Average waveforms to real words recorded in the “front” and “back” positions for one subject are superimposed. The left panel shows two gradiometer sensor pairs. Sensors over the left frontal area show larger evoked fields in the “front” position. Conversely, the evoked fields picked up by the posterior sensors are stronger in the “back” position.

DISCUSSION

These results indicate that the head position in the whole-head MEG helmet has a significant effect on the sensitivity to the sources in the anterior regions of the brain. Because the strength of the magnetic field decreases with the square of the distance, it is important to position the brain sources of primary interest as close to the sensors as possible. A device (such as a bite-bar) that helps the subject to fix his/her head comfortably in a particular position, to maintain the same position throughout the run and minimize motion artifacts seems to be essential in achieving that goal [Adjarian, 2004]. In cognitive tasks, particularly those involving language, the fronto-temporal regions may be of utmost interest to a researcher as they subserve semantic and mnemonic processing of both spoken and written words as suggested by MEG [Marinkovic, 2003], functional neuroimaging [Fiez, 1998], and intracranial studies [Halgren, 1994]. This may be particularly critical for the N400m (magnetic equivalent of the “N400”), which indexes semantic and contextual integration, or access to meaning [Halgren, 2002]. Previous MEG studies of language relying on the distributed aMEG approach [Dhond, 2001, Marinkovic, 2003] indicated left temporo-prefrontal regions as the main N400m sources, whereas the MEG studies utilizing the ECD approach estimated the main dipole in the superior posterior temporal area [Helenius, 1998] [Sekiguchi, 2001]. The differences could be explained by the respective source modeling techniques [Halgren, 2002], but also potentially by the head position in the helmet. The commonly adopted “back” position may put the anterior sources at a disadvantage because of the increased distance between the brain and the sensors. In sum, these results emphasize the need to adjust the head position in the helmet in order to maximize the “visibility” of the sources in the anterior brain regions in cognitive and language tasks.

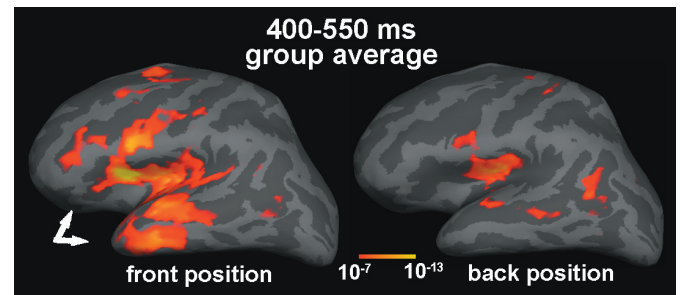


Fig. 3. Averaged dSPMs to word-specific activity observed during the “front” and the “back” head position runs

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MEG Evidence for Phonological Underspecification

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ABSTRACT

Subjects ($n=12$) listened to the synthesized syllable tokens [ba], [da], [ma], and [na]. Evoked magnetic fields were recorded using a 93-sensor whole-head biomagnetometer array while subjects performed a same-different judgment task. An underspecification model of phonology predicts an asymmetry such that coronal deviants should elicit greater MMFs than labial deviants, while other models do not. This asymmetry is exactly what we observe ($F(1,11)=7.218$, $p=.02$), thereby supporting the existence of maximally abstract linguistic mental representations.

KEY WORDS

language, speech perception, phonology, underspecification, consonant, coronal

INTRODUCTION

Underspecification models, such as the Featurally Underspecified Lexicon (FUL), maintain that phonological representations are maximally abstract, so that not all phonological features are stored [Steriade, 1995] [Lahiri and Marslen-Wilson 1991]. The English consonant pairs /m/-/n/ and /b/-/d/ provide an example of such a case. The place of articulation feature [LABIAL] is assumed to be specified in English in the FUL model, while [CORONAL] is not. Thus the presence of the [CORONAL] feature in an acoustic token of [d] conflicts with the underlying [LABIAL] specification of /b/. But the [LABIAL] specification of surface [b] does not conflict with underlying /d/, since underlying /d/ does not have a place specification.

A sizable body of evidence has accumulated for this viewpoint in the linguistic literature [Lahiri & Reetz, 2002]. Eulitz *et al.* [2003] present neurobiological evidence as well, using EEG to measure the mismatch negativity (MMN) response to vowel pairs. In this study we investigate the same question, using the consonant pairs discussed above and the MEG correlate of the MMN (the mismatch field response, or MMF). Previous studies have shown that the MMN/F is sensitive to language-specific phoneme representations, and to abstract featural phonological properties in preference to acoustic difference [Näätänen *et al.*, 1997] [Sharma & Dorman, 1999] [Phillips *et al.*, 2000].

METHODS

Seventeen subjects participated and gave informed consent, all right-handed MIT affiliates with no history of hearing or neurological disorders, including 9 males and 8 females. Eleven were native speakers of English, five of other languages (Czech (2), Spanish, Russian, and Persian) but fluent in English. One subject was later excluded due to technical problems, three because they did not display the field distribution associated with the MMF during the appropriate time window, and one (Argentinian Spanish speaker) because his mismatch peak fell outside of two standard deviations from the mean. Stimuli consisted of one token each of four CV syllables – [ba], [da], [ma], [na] – synthesized with the formant-based synthesizer HLSyn [Stevens & Bickley 1991] [Hanson & Stevens, 2002] [Klatt & Klatt, 1990]. Stimulus syllables were correctly identified and discriminated by speakers.

Subjects lay supine in a magnetically shielded room while stimuli were presented binaurally over earphones. Evoked magnetic fields were recorded using the MIT/KIT whole-head biomagnetometer array, with 93 axial gradiometers for ~25 minutes/subject. Subjects first listened to a 1kHz tone presented 100 times, then performed a mismatch detection task (oddball paradigm). Four identical precursor stimuli, with inter-stimulus intervals of 400 ms, were presented, then a fifth stimulus, either identical to the previous four (control condition or *standard*), or differing in place of articulation of the initial consonant (*deviant* condition). This resulted in eight conditions, which subjects heard 30 times each. Trial presentation was randomized by Psyscope script [Cohen *et al.*, 1993] and divided into six blocks of forty trials, with breaks of subject-determined duration between blocks. Subjects were instructed to press one button when the final set item was the same as the previous ones, and a second button if it was different.

Data were sampled at 1000 Hz, with acquisition between 1 and 200 Hz. The raw data was then subjected to a noise reduction routine to eliminate measured magnetic activity from external sources. Responses to stimuli were averaged by stimulus condition separately, in 700 ms windows keyed to the onset of the stimulus: 100 ms pre-, 600 ms post onset. The averaged signal was subjected to a low-pass filter below 30 Hz and adjusted to baseline using a 100 ms pre-stimulus interval. Amplitudes and latencies of the MMF component were recorded by calculating the root mean square (RMS) field strength from sensors covering the field pattern of the MMF/M100 in the left hemisphere. Sensors were selected for each subject by creating a grand average of all 8 conditions and choosing six sensors, divided evenly between source and sink, that showed the clearest dipolar distribution and held constant across conditions within a subject with visual inspection. The RMS of each deviant condition was compared to that of the corresponding standard (e.g., the [da] response following a series of [ba] to the [da] response following a series of [da]).

RESULTS

A one-way repeated measures ANOVA yields no significant difference in the average amplitude of the RMSs for the labial versus coronal mismatch condition in the 0-199 ms post-stimulus onset time window ($F(1,11)=.57$, $p=.47$). However, in the MMF time window of 200-300 ms, a significant difference did appear ($F(1,11)=7.22$, $p=.02$). Latency of the mismatch peak showed a trend toward being earlier for coronal deviants than for labial deviants, though this tendency did not reach significance ($F(1,11)=2.72$, $p=.13$).

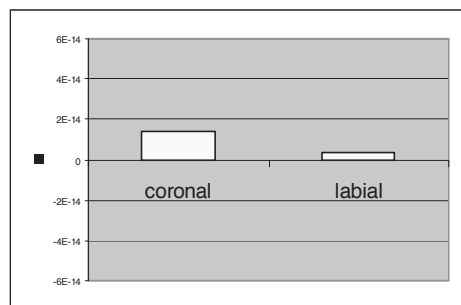


Figure 1. Group MMF amplitudes averaged over 200-300 ms window.

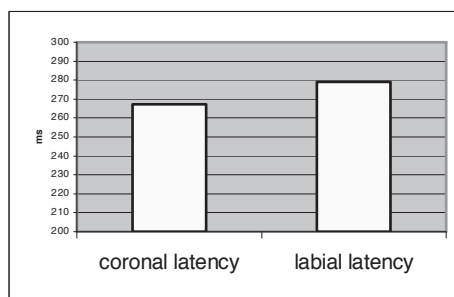


Figure 2. Group MMF peak latencies.

articulation specification, but in whether such a specification is present at all. Models of phoneme representation in the mind which depend solely on acoustics and/or fully-specified representations fail to account for the asymmetry observed here in perception of consonant pairs. This suggests that differences in degree of phonological specification exist and are relevant in speech processing.

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DISCUSSION

The stimulus pair [ba]/[da] is acoustically equidistant regardless order of presentation—likewise for [ma]/[na]. They might be expected, therefore, to evoke a mismatch response of similar amplitude and latency regardless of ordering. Instead we find that a significant difference does appear for amplitude, and a trend towards a distinction in latency. Following Eulitz *et al.* [2003], we hypothesize that these differences are due to comparisons being made between representations that differ not just in place of

Spatiotemporal analysis of neuromagnetic activation associated with mirror reading

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ABSTRACT

Our previous report has confirmed that visually presented words can elicit neuromagnetic activities from the visual cortex, angular gyrus and Broca's area. It is not clear how the words are visuospatially transformed and recognized by the human brain. Mirror reading is characterized by reading which runs in the opposite direction to normal reading, with reversals of letters. It would be very interesting to find out if there are any neuromagnetic differences between the mirror reading and normal reading. Four right-handed healthy adults have been studied with a whole cortex Magnetoencephalography (MEG) system. The stimuli consisted of eight normal oriented words and eight "reversed words" (mirror-image of the words). All stimuli were randomly presented on the screen in front of the subjects using DirectX. MEG data were analyzed using both single dipole modeling and synthetic aperture magnetometry (SAM). Four responses to the reversed words were identified in all four subjects. In comparison to the normally oriented words, the reversed words elicited a stronger response at a latency of 248 ± 6 ms. SAM results indicated that the reversed words invoked strong activations in the left and right parietal cortices but the normally oriented words did not. The mirror reading elicited one magnetic response which is different from that of the normal reading. The difference between the mirror reading and the normal reading in terms of neuromagnetic activation may reflect the development of novel representations for reversed words.

KEY WORDS

Magnetoencephalography (MEG), language, word, mirror reading, visual evoked magnetic field, brain, synthetic aperture magnetometry (SAM)

INTRODUCTION

Mirror reading has been considered to be involved in the learning of perceptual skills [Poldrack, 1998]. The learning of perceptual skills is thought to rely upon multiple regions in the cerebral cortex, but imaging studies have not yet provided evidence about the changes in neural activity that accompany visual skill learning. Functional magnetic resonance imaging (fMRI) has been used for the studies of mirror reading in recent years [Poldrack, 2001]. The results of fMRI studies indicate that multiple regions in the occipital lobe, inferior temporal cortex, superior parietal cortex and cerebellum are involved in the reading of mirror-reversed text. Learning to read mirror-reversed text involves a progression from visuospatial transformation to direct recognition of transformed letters [Dong, 2000].

MEG is well suited for studies of language processing because it allows non-invasive brain recordings in normal subjects with good spatial resolution and excellent temporal resolution. To reveal the frequency-dependent volumetric distribution of language evoked magnetic fields, we used the synthetic aperture magnetometry (SAM) in this study. SAM directly localizes frequency specific changes from the unaveraged MEG signals. Using unaveraged MEG signals is much better than using averaged MEG signals because averaged evoked response to language stimulation may appear attenuated and distorted by the naturally occurring variations in latency and activation pattern [Xiang, 2001].

Our previous report has confirmed that visually presented words can elicit neuromagnetic activities from the visual cortex, angular gyrus and Broca's area. It is not clear how the mirror-reversed words are visuospatially transformed and recognized by the human brain. To our knowledge, MEG has not been used for the study of neuromagnetic mechanisms underlying mirror reading. This study focused on the neuromagnetic activation associated with reading mirror-reversed words. Building on our previous results [Xiang, 2001], the objective of this study was to investigate the neuromagnetic spectral distribution of mirror reading.

METHODS

Subjects: Four right-handed healthy adults (1 women and 3 men, aged 26 – 39 years, with a mean age of 31 years) were studied. All subjects were free of known neurological disorder, and had normal vision. Informed consent for the study was obtained from all subjects.

Stimuli: The stimuli consisted of eight normal oriented words and eight mirror-reversed words. Words were composed of four to six letters (e.g., apple, water). All normal oriented words and mirror-reversed words were mixed and randomly presented on the screen in front of the subjects. Each was repeated 20 times for a total of 320 stimuli per session. Stimuli were presented in random intervals. They were shown for 1000 ms, long enough to be perceived by subjects. The participants were asked to view the words silently. To provide high quality visually presented stimuli, a novel visual stimulation system using DirectX was developed.

MEG recordings: A 151-channel whole cortex CTF OMEGA system was used for recordings (CTF Systems Inc., Port Coquitlam, Canada). The MEG measurements were performed in a MSR with a total system white noise level below $10 \text{ fT}/\sqrt{\text{Hz}}$. The localization of the subject's head relative to the sensor array was measured using three small coils affixed to the nasion and pre-auricular points. The sampling rate of data acquisition was 1250 Hz. An acquisition window was 1000 ms, with 100 ms pre-trigger. The analysis window was 100 ms before and 600 ms after the stimuli.

MRI scans: Three-dimensional magnetic resonance imaging (MRI), 3D-SPGR sequence, was obtained for all subjects using a Signa Advantage (GE Medical System, Milwaukee, USA).

Data analysis: Six frequency bands were analyzed including 0.5 – 4 Hz, 4 – 8 Hz, 8-15 Hz, 15-30 Hz, 30 – 60 Hz and 60-125 Hz. A real head model was produced from each subject's MRI, and multiple spheres were used in SAM analysis. The region of interest (ROI) was set to include the whole brain with a 5 mm voxel resolution. The resulting volumetric data were then automatically scanned for peak areas of the changes. The center of the peak area was identical to the equivalent current dipole (ECD) for the averaged MEG data. SAM allowed for localization to an accuracy of better than 5 mm. The distributions of spectral power were displayed on the individual MRI using a software package called magnetic source locator (MSL) [Xiang, 2001].

RESULTS

The averaged magnetic waveforms showed four clear deflections (Figure 1). Four responses to the reversed words were identified in all four subjects (4/4). In comparison to the normally oriented words, the reversed words elicited a stronger response at a latency of 248 ± 6 ms. The contour

maps of the four main responses indicate a single dipole pattern. Dipole based source localization showed the neuromagnetic activities were generated from the occipital and parietal cortices (dipole fitting error < 20%).

SAM results showed that the spectral distributions in the 0.5-4 Hz, 4-8 Hz and 8-15 Hz bands varied among subjects. In contrast, the spectral distributions in frequency bands above 15 Hz were reproducible. The SAM images in 15-30 Hz frequency band showed a clear decrease in spectral power (desynchronization or suppression) near the right and the left occipital cortices. However, there was no significant difference between the mirror reading and normal reading in this frequency band. In the frequency band of 60-125 Hz, a clear increase in spectral power at the junction of the parietal and occipital cortices was identified in all subjects. A significant decrease in spectral power around the junction of the left inferior frontal and precentral gyri (Brodmann area 44 and area 6) was also observed in 3 subjects. In comparison to normal reading, mirror reading had stronger neuromagnetic activities in the parietal and occipital cortices.

The most interesting result was the clear neuromagnetic activities in the left and the right parietal and occipital cortices in the frequency band of 30–60 Hz during mirror reading (Figure 1). The focal changes were consistent across all subjects (4/4). In comparison to normal reading, mirror reading evoked much stronger and clearer activities in both hemisphere, particularly, the left and right parietal and occipital cortices. This was significantly different from the neuromagnetic activities evoked by normal reading which were mainly generated from one hemisphere (three in the left and one in the right).

DISCUSSION

The results of the fMRI studies suggested that the bilateral superior occipital gyri, bilateral superior occipital gyri, bilateral middle occipital gyri corresponding to Brodmann area (BA) 18/19, bilateral lingual gyri (BA 19), left inferior occipital gyrus (BA 18), left inferior temporal cortex (BA 37), bilateral fusiform gyri (BA 19), right superior parietal cortex (SPC) (BA 7), left

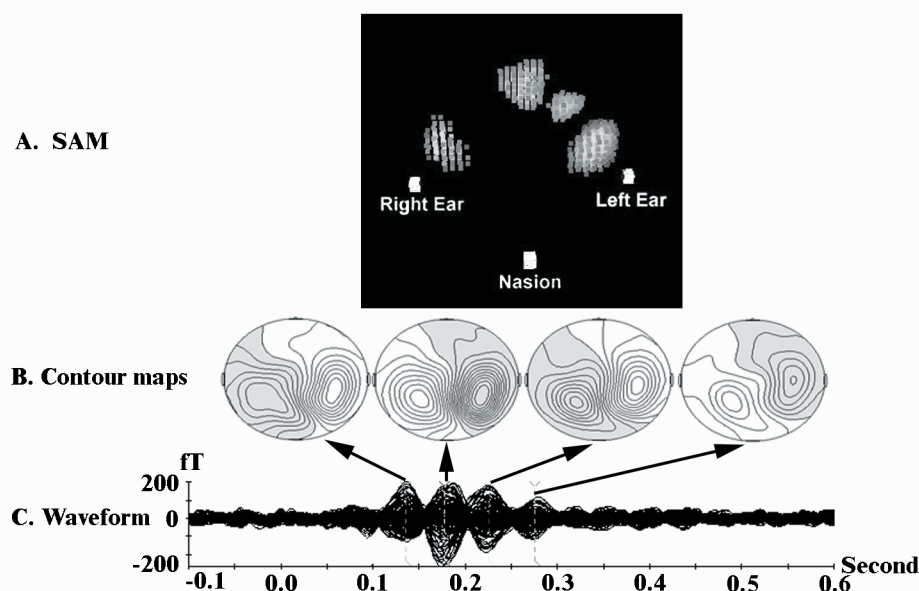


Figure 1. Neuromagnetic activation associated with mirror reading. **A.** Three-dimensional SAM image indicates the reconstructed the volumetric functional regions related to mirror reading using unaveraged magnetic signals. The most interesting finding is the clear activation in the left and right parietal cortices. **B.** Contour maps indicate the dipole patterns; clearly, the main activities are generated from occipital and parietal cortices. **C.** Averaged magnetic waveform show four deflections (responses). The arrows point to the corresponding contour maps.

inferior frontal gyrus (BA 44/45) and an inferior part of the left BA 6 are involved in mirror reading [Dong, 2000; Poldrack, 2001]. However, which brain areas are essential for the processing of mirror reading is still unknown.

To our knowledge, MEG has not been used for the study of mirror reading. Our results demonstrated that mirror reading evoked four clear responses. One response was significantly stronger than the corresponding neuromagnetic waveform elicited by the normal reading. This study has identified the brain areas involved in mirror reading. In comparison to the normal reading, mirror reading evoked stronger activities from the bilateral occipital and parietal cortices. The difference between the mirror reading and the normal reading in terms of neuromagnetic activation may reflect the specific brain processing for mirror reading. We consider that neural processing of mirror reading might require an interaction of visuospatial transformation and linguistic recognition. The neuromagnetic activities in the occipital and parietal cortices may reflect the processing for the visuospatial transformation, which is required for the accurate recognition of mirror-reversed words.

ACKNOWLEDGEMENTS

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MEG Evidence that Age of Language Learning Does Not Matter

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Some recent imaging results have suggested significant differences in neural localization between early- and late- bilinguals [1]. However, none of these studies systematically controlled for proficiency levels in the target language evaluated, linguistic relationship between the native language and the target language nor for the precise nature of the dependent linguistic factor evaluated.

In this paper, we report results from a new MEG study that compared neurological patterns between Spanish/English and English/Spanish bilinguals at each of two proficiency levels in the second language (Intermediate and Advanced). By exploiting the syntactic differences of ordering and agreement between Spanish and English, we investigated learners' ability to differentiate between grammatical and ungrammatical adjective-noun ordering and agreement and subject-verb agreement. The behavioral measurement of reaction time, as well as the neural evoked response component at 600ms after the onset of visually presented material (M600, a neurological component arguably associated with syntactic processing). Our results indicate, in contrast to earlier reported results that: i) independent of when a new target language was learned, the more proficient (as measured by independent standardized tests) a speaker becomes in a new language the more the neurological patterns resemble those isolated for monolingual native speaker controls and ii) at all levels of proficiency neurological evidence that the subjects utilize structure dependent rather than structure independent processing mechanisms in the computation of the linguistic stimuli.

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Compound words and structure in the lexicon: an MEG investigation

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We investigated the representation and processing of morphologically complex words (noun-noun compounds, e.g. teacup) in the mental lexicon, contrasting theoretically motivated claims about their internal structure. Under non-decompositional analyses, compounds are treated as atoms on par with single words (e.g. station). In contrast, decompositional accounts posit internal structure for compounds (teacup=tea+cup). Our results using magnetoencephalography (MEG) during visual lexical decision to compounds, single words, nonwords (e.g. nishpern) and word-nonword foils (e.g. crowskep) suggest structured representations for compounds and early online decomposition. Twelve monolingual English speakers responded to 60 disyllabic noun-noun compounds, 60 pairwise-matched single words, 104 nonwords and 16 word-nonword foils, while a 160-channel whole-head MEG system (Kanazawa Institute of Technology, Japan) recorded brain signals. The compounds and single words were matched on overall properties influencing processing (length/frequency/syllabicity), but the compounds' parts were shorter, higher-frequency, and monosyllabic. Thus, decomposition predicts an advantage for compounds, but non-decompositional accounts predict no differences. Only early decomposition predicts both initial MEG divergence and response time (RT) facilitation. Both RT and the first significant divergence in peak latency in the MEG signal (350 ms post-onset, M350) were earlier for compounds, supporting early decomposition. RT to foils was accurate but delayed relative to compounds, single words and nonwords, showing that the compound effect is not simply word finding (all reported effects $p < .01$, two-tailed paired t-test). The results suggest morphologically complex items are internally structured entries in the mental lexicon. We discuss extensions of this approach, examining lexical-semantic structure and the role of structure in acquisition.

Hemispheric language dominance in patients with focal epilepsies: a prospective MEG study

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Previous studies have shown that 94% of healthy right-handed subjects were left hemisphere dominant for language, but that a higher degree of atypical language representation was shown in patients (pts) with epilepsy [1]. In this study we prospectively investigated hemispheric language dominance (HLD) with MEG in 22 right-handed epilepsy pre-surgical candidates with medically intractable focal epilepsies. Methods: 22 pts, aged 11 – 61 years underwent MEG language mapping during their pre-surgical evaluation using whole-head 306-channel MEG (Elekta-Neuromag) and simultaneous EEG. A visually presented verbal reading task was used. Equivalent Current Dipoles (ECD) were fitted hemisphere by hemisphere using sequential single dipole fitting with a time range of 150ms – 600ms and time step of 1ms. The Laterality Index (LI) was calculated for each pt [2]. WADA Test results were obtained for 11 of the 22 pts. Results: Using MEG, 15 pts (68.2%) showed left HLD, 2 pts showed Right HLD (9%), and 5 pts showed Bilateral HLD (22.7%). WADA results were concurrent in 8 pts, showing a Left HLD. One pt showed a Bilateral result for the WADA test and the result from MEG was completely Left HLD. Three of five the pts that showed Bilateral HLD with MEG showed Left Hemisphere Dominance with the WADA test. Conclusion: MEG seems to be a promising method for the determination of hemispheric language dominance in patients with focal epilepsies.

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Magnetic Responses to Visually Presented Words with Masked Repetition Priming

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We investigated the effects of repetitive presentations on neural processing of visually presented words. A string of mask pattern “#”, a character string (prime), and a word (target) were sequentially displayed with a three-field paradigm; the mask pattern was replaced by primes which lasted for 70 ms, and then replaced by targets which lasted for 100 ms and 1000 ms in two sessions. The target words consisted of five Japanese katakana (syllabogram) characters, while the primes consisted of five Japanese hiragana (syllabogram) characters that had the same sounds as the following target words (repetition priming) or consisted of five pseudo-characters (control), which were made by deforming katakana characters. Subjects were required to judge whether the target words belonged to the category informed before and to respond by pressing yes or no button. 320 magnetic responses were recorded with a whole-head 148-channel MEG system (BTi) from 500 ms before to 1500 ms after the target words appeared. The average waveforms included slowly-varying components which lasted as long as 1000 ms for each of four conditions (two targets (yes or no) x two primes (repetition or control)). In two cases of eight (four subjects times two sessions), reaction time for the affirmative (and correct) answers was significantly shorter by 66 ms and 76 ms for the repetition priming condition than for the control condition. For the two cases, the measured magnetic responses had small differences in field distributions in the left or right temporal areas in a latency range from 400 to 600 ms, which preceded the reaction time by 100 or 400 ms. They may reflect difference in neural processing, which was influenced by the prime words in comparison with the pseudo-character strings.

Pure alexia in stroke patients measured by MEG utilizing MR-FOCUSS

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Visual word recognition may be impaired following stroke, as in the syndrome “pure alexia” wherein other cognitive-linguistic functions are largely spared. Patients with this disorder often use a laborious strategy of reading letter-by-letter (LBL) despite some residual whole-word reading ability. The characteristic lesion site associated with pure alexia has been identified through structural analyses (i.e., left occipital cortex involving the splenium of the corpus callosum), but functional analyses of the time course of brain activation underlying this disorder have not been reported. It remains unknown why some LBL readers show covert processing of whole words and others do not. It is also controversial whether LBL reading reflects weak activation of the left hemisphere reading system or a right hemisphere compensatory reading system. In this initial study, we determined the current density mapping response using MR-FOCUSS in 2 patients with pure alexia and 4 control subjects. MEG responses were recorded during a speeded visual matching task in which participants made same/different judgments and responded via button press. Stimulus conditions of words versus false font strings were compared. In control subjects, letter identification for word stimuli localized to the left hemisphere, whereas identity and position analysis for false font stimuli localized to the right hemisphere. In contrast, for LBL readers letter identification in word matching involved bilateral activation. Moreover, right hemisphere activation early in the time course of word matching (105 msec) in the LBL readers occurred in the same region activated in false font matching in the control subjects. These findings support the idea that right hemisphere reading may support covert global reading of whole words in patients with pure alexia, while the weakened left hemisphere supports local LBL reading. **Supported** by NIH/NINDS Grant RO1-NS30914

Semantic Contextual Effects on Early Neural Activities for Visual-Word Processing

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To investigate semantic contextual effects on early stages of visual-word processing, MEGs were recorded by related and unrelated prime-target pairs during a categorical decision task. The pair stimuli (Japanese katakana characters; syllabogram) were presented for 100 ms in the left or right visual field, and stimulus onset asynchrony between prime and target was made to be 1000 ms. In categorical match trials, mean reaction time was 724 ms and 808 ms for the related and unrelated conditions respectively. After the target presentation, MEGs had four components (~ 300 ms) and consecutively a slowly-varying component in both related and unrelated conditions. The first and second components were detected in the occipital visual areas along the ventral visual processing streams in the left or right hemisphere contralateral to the presented stimuli (100 and 150 ms), and the third component spread around the superior-anterior temporal and inferior frontal areas in the left hemisphere (210 ms). As the following period, the fourth component mainly converged again around the occipital areas, while the other areas were also activated (260 ms). The amplitude for the related condition was larger than that for the unrelated condition for the second component as well as the fourth. These results suggest that activity in the temporal and inferior frontal cortices was connected with visual word processing during its early stages, and activities in the visual cortices were intensified by the semantic contextual effect, which was derived from the related prime word. They support an idea that semantic top-down information modulates the neural activities for the occipital cortex in the early period.

SAM analysis of focal oscillatory change induced by silent reading

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Time-frequency distribution of cortical oscillatory change induced by silent reading was investigated using Synthetic aperture magnetometry (SAM). Subjects were instructed to read visually-presented hiragana words without phonation only once immediately after the presentation of a word. Locations of cortical oscillatory changes were estimated by SAM statistical imaging with peak value of t statistics between control and active state. Intracortical currentdensitograms of the locations of oscillatory changes were estimated by the SAM virtual sensor. Time-frequency spectrograms of cortical oscillatory change were made from the currentdensitogram using MatLAB. Time-frequency spectrograms demonstrated detailed characteristics of cortical oscillatory changes in the language-related areas. The results were consistent with the rough time-course in our previous study [1]. Time-frequency analysis may contribute to elucidate dynamic mechanisms of task-related cortical oscillatory change.

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Right hemisphere beta and posterior alpha oscillations are modulated in a language comprehension task

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Even though event-related potentials/fields (ERP/Fs) have led to important insights on language processing, relevant information may also be contained in oscillatory responses not phase-locked to the stimuli. The aim of this study was to explore oscillatory responses elicited in a classical 'N400-paradigm'. Sentences in which the last word was inappropriate in the sentence context (semantically incongruent) were presented auditorily and compared to congruent sentences. Brain activity was recorded from 10 participants using a 151-sensor MEG system (CTF) and the data were converted to the planar gradient. As reported by others, we observed a left lateralized ERF over temporal regions peaking ~300-500 ms. This N400m was stronger for incongruent than congruent sentence endings. In response to incongruent sentence endings, strong beta activity was observed over the right hemisphere ~1 s after the last word. Over posterior areas we observed stronger alpha activity for the incongruent than for the congruent sentence endings. A SAM analysis localized the source of the beta increase in the right hemisphere around the posterior part of the Sylvian fissure. We suggest that the late right-hemisphere beta increase and the posterior alpha increase following incongruent sentences endings reflect suppression of brain structures not involved in language comprehension. The suppression frees resources for application to left-hemisphere language areas.

Form vs. Meaning in Visual Word Recognition: An MEG study using Masked Priming

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Masked Priming has been used in behavioral studies to dissociate the effect of form (orthography and/or morphology) and meaning in visual word recognition. The goal of this study is to establish the neural correlates of this dissociation using MEG. Following [1], we presented masked primes (duration; 34ms) to 12 subjects and measured RT on the target words in a lexical decision task. Experiment 1 tested priming with unrelated, identical, vs. semantic primes. We replicated the behavioral results in [1]: priming by identical primes; no priming by unrelated or semantic primes. Preliminary analysis of the MEG measurements show a shorter latency at the M170 for identity priming, with no difference between unrelated or semantic primes. Experiment 2 tested priming with morphological vs. orthographic primes. Based on Experiment 1 and [2], we hypothesized that morphological decomposition applies blindly to all *potentially* complex words. Any target-prime pair differing only by a letter string that can be a morpheme was considered morphologically related. The behavioral results showed priming in both morphological and orthographical conditions, replicating [2]. We expect to find a neural correlate of morphological priming in the latency of the M170. This study shows that the M170 reflects masked form priming effects that are activated before the lexical meaning is accessed.

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Magnetoencephalographic Study of Written Chinese Word Processing

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To study the cortical semantic processing of written Chinese words, we used 2-word verbs and corresponding meaningless pairs produced by replacing the second words (W2) of corresponding verbs with their homophones. Fourteen right-handed healthy adults viewed word pairs randomly presented one word at a time and judged the semantic appropriateness of W2 to the preceding first word (W1). We measured magnetoencephalographic (MEG) responses to W1, congruous W2, and incongruous W2 during semantic judgment task or non-judgment condition. Multidipole analyses revealed common activations across subjects sequentially involving bilateral visual cortices at ~100 ms, bilateral occipitotemporal regions at ~190 ms, and the left temporal lobe at ~400 ms. In the 8 subjects with bi-temporal responses, the dominant semantic activation occurred on the left side in terms of larger amplitude and earlier peak latency. Compared with W1 and congruous W2, incongruous W2 elicited clearly larger semantic activation: N400m responses localized in the left mid-superior (10 subjects) or anterior-mesial temporal lobe (4 subjects). Albeit no direct relation to the discrimination of word congruity, the left occipitotemporal activation was larger during semantic task than non-judgment condition, implying a crucial role of this area in word structure analysis.

Key Words: semantic processing; written Chinese words; MEG; language; N400m; visual.

Categorization of Speech and Non-speech Sounds: An MEG study

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We investigated perception and categorization of simple speech and non-speech auditory stimuli employing a delayed match-to-sample paradigm. Four kinds of stimuli were used: pure tones, tonal contours (TC), vowels and consonant-vowel syllables (CV). Each kind of stimulus had 2 categories, each containing 3 examples. The categories for speech stimuli were natural categories; non-speech categories were newly defined and learned by the subjects during training. Brain activities were recorded using a 160-channel whole head MEG system while subjects were performing tasks. They listened to two sounds and decided if they sounded exactly the same in auditory discrimination condition (AUD), or if they belonged to the same category in category discrimination condition (CAT).

We analyzed the MEG data using an induced wavelet transform method. In auditory cortex, for both AUD and CAT conditions, an alpha (8-13Hz) band activation enhancement during the delay period was found for all the stimuli. In auditory cortex, a CAT-AUD difference was found only for the non-speech stimuli, whereas in frontal areas, the difference existed for both speech and non-speech stimuli. These results suggest that alpha band activity in auditory cortex is related to both short-term memory and categorization. Importantly, the CAT-AUD dissociation between speech and non-speech occurred in auditory areas and not in frontal areas, suggestive of the presence of different categorization mechanisms and networks for newly learned (non-speech) and natural (speech) categories.

Intensive language training enhances brain plasticity in chronic aphasia

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Focal clusters of slow wave activity in the delta frequency range (1-4 Hz) as measured by magnetencephalography (MEG) are usually located in the vicinity of structural damage of the brain. In the present study we investigated the change in Delta Dipole Density (DDD) in 28 patients with chronic aphasia (> 12 months after stroke) following cerebrovascular stroke of the left hemisphere before and after intensive speech and language training. Evaluation criteria included neurolinguistic testing (Aachen Aphasia Test Battery), brain imaging was performed using MEG, coregistered with structural magnetic resonance scans (MRI).

The 28 patients received 30 hours of intensive language training over a period of 2 weeks (3 hrs./day). Neuropsychological testing and MEG assessment were performed before and after therapy. Patients improved on average after therapy and single case analysis revealed significant improvements in about 85% of the patients. Perilesional dysfunctional slow wave activity decreased in about 60% of patients that improved in the AAT, which might be an indicator of re-recruitment of these areas. An increase of perilesional activity in 9 patients with improved language functions might be explained by further segregation of dysfunctional components from the speech network with correspondent slow wave synchronisation. Changes in global measures of aphasia severity (AAT profile score & Token Test) varied with magnitude of change only in left hemispheric DDD. These results emphasize the impact of perilesional areas in the rehabilitation of aphasia even years after the stroke and might reflect reorganisation of the language network that provides the basis for improved language functions after intensive after intensive training.

MEG investigation of phonological processing during reading in children and adults

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Phonological processing is an important skill in reading acquisition [1]. The goal of the present study is to better understand the cortical activity related to the development of phonological skills. To this end, normal adults (20-30 years of age) and children (8-12 years) were presented pairs of nonwords for rhyme judgment using a 'same' versus 'different' response choice. Stimulus pairs were presented visually for a maximum duration of 5000 ms, or until the subject responded. Brain responses were recorded using a 306-channel whole-head MEG system. Cortical sources of the averaged evoked responses were modeled as equivalent current dipoles (ECD). Whereas both groups of subjects were able to do the task (>70% accuracy), the children had longer response latencies. This was evident in the source activity, which persisted for a longer period of time in children than in adults. However, both ECD and MNE analyses revealed similar areas on activation for the two groups; these included extrastriate, inferior frontal, and temporal areas. Interestingly, though, children showed a tendency towards more frequent changes in activation foci, within and across hemispheres, while doing the task. Taken together, these preliminary findings may suggest ongoing phonological development in this age group, which can have important implications for understanding activation patterns in children with reading disabilities. Supported by NIDCD, The Whitaker Foundation, and the MIND Institute. [1] Mody, M. 2004. Neurobiological Correlates of Language and Literacy Impairments. In Stone et al., (Eds.), Handbook of Language and Literacy: Development and Disorders, NY: Guilford Press.

Neuromagnetic Responses to Words Presented in Peripheral Visual field

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Peripheral vision plays an important role in reading natural sentences. In this work, we measured MEGs using word and non-word stimuli presented in central and peripheral visual fields. The words consisted of five Japanese katakana characters (syllabogram), while the non-words were made by changing one character of words. They were vertically arranged and randomly presented during 100 ms at one of six locations having 1°, 5°, and 9° eccentricities to the left or right from a fixation mark. Two normal subjects participated in the experiments. They were instructed to press yes or no button depending on whether they detected word or not, where no button means that they detected a non-word or they failed to detect. Mean reaction time was 615 ms and 696 ms for yes and no button respectively, and mean hit rate was 80% for central (1°) stimuli. The hit rate decreased to about 50% for peripheral (5° and 9°) stimuli, reflecting that visual acuity was reduced. We observed MEG peaks at latencies earlier than 200 ms (I), one or two peaks at latencies of 200 to 300 ms (II), and a slowly-varying component in a latency range from 300 to 800ms (III). The amplitude was smaller for peripheral stimuli than for central stimuli in both of case (I) and (III). However field distributions were different between the central and peripheral stimuli, and between the left and right visual stimuli for (I), but there were no differences between them for (III). No systematic differences were observed for case (II). The results showed that neural activity was smaller for the peripheral stimuli than for the central stimuli in early and late latencies, as the character recognition became worse.

Morphological Decomposition in Hebrew Verbs: An MEG Masked Priming Study

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The M170 component is reliably found in ERP and MEG studies of lexical access and is thought to be a correlate of visual word-form recognition [1]. Behavioral masked priming studies reveal that morphological relatedness (but not phonological or semantic similarity) facilitates reaction time in lexical decision tasks. In behavioral masked-priming, facilitation effects have been found for morphological identity [2]: Hebrew verbs in the same *binyan* (conjugation class), such as 'gidel' (he grew) and 'diber' (he spoke) primed each other. The goals of this study were twofold: 1) to identify an MEG correlate for the morphological identity facilitation effect and 2) to add a condition to dissociate morphological identity from phonological relatedness. To this second end, we examined priming between 'gidel' (he grew) and 'tedabru' (you-pl. will speak), which diverge phonologically but share an abstract morphological identity through the *binyan*. Preliminary results from 7 subjects suggest that there is in fact an MEG correlate for morphological priming: shared identity evokes a single peak M170 component, while an unrelated prime evokes two temporally distinct peaks at the same region. Furthermore, the novel condition, with identical *binyan* but divergent phonological form, evokes the single peak characteristic of identity. We aim to verify these preliminary findings through further testing. The predicted results are significant both in establishing M170 as a component sensitive to the morphological structure of visually presented words and in establishing the status of conjugation classes in Hebrew as integrated perceptual units of word form.

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Speech intervention affects brain activity in bilingual language impaired children

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We studied the effect of a new intervention program on speech discrimination in bilingual children with specific language impairment (SLI). The effects were assessed by behavioural measures and brain activity recording with magnetoencephalography (MEG). Subjects were bilingual (Finnish-Swedish) preschool children (mean age 6 years 7 months). Two sets of syllables (/su/ as standard, /so/ and /sy/ as deviants, and /da/ as standard, /ba/ and /ga/ as deviants) were used as stimuli in the oddball paradigm. The initial MEG measurement and behavioral test on sound-pair discrimination were followed by an intervention period of 8 weeks, after which MEG and behavioural tests were administered again. Half of the SLI children served as a control group and participated in a physical exercise program. The language-intervention group improved on behavioural sound discrimination. In their brain responses the rehabilitation effect was manifested in two different ways. After the intervention, equivalent current dipoles of P1m at 213 ms evoked by /ba/-deviant became stronger on both hemispheres. In addition, dipole moments of P1m after /ga/ (at about 210 ms) were increased in the right, and those of MMNm after /sy/ (at about 520 ms) in the left hemisphere. The results indicate that children who received language-related intervention improved in discriminating sounds, and this positive rehabilitation effect was reflected in their brain activity.

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An MEG correlate of word recognition

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A fundamental challenge for the cognitive neuroscience of language is to capture the spatio-temporal patterns of brain activity that underlie critical functional components of the language comprehension process. We combine here psycholinguistic analysis, whole-head magnetoencephalography (MEG), the Mismatch Negativity (MMN) paradigm, and source localization techniques (Equivalent Current Dipole and L1-Minimum-Norm Current Estimates) to locate the process of spoken word recognition in space and time.

Methods: MEG signals were recorded with a 306 MEG system (Vectorview, Elekta Neuromag, Helsinki) while subjects instructed to ignore acoustic stimuli watched a silent movie of their own choice while being presented with spoken words of Finnish. Words were presented in an oddball design, either as frequent standard stimuli ($p = .17$) or as rare deviant stimuli ($p = .83$). Two spoken words starting with the same consonant and vowels, but ending in different consonants, were submitted to psychophysical and psycholinguistic experiments to determine (a) when they became perceptually different and (b) at which exact point in time after their onset each of them could be recognized ¹. Stimulus triggered averaged event related fields, ERFs, were calculated for each subject and each standard and deviant stimulus word. The magnetic Mismatch Negativity, MMNm, was calculated by subtracting the averaged standard ERF from the deviant ERF. Source localization was performed using equivalent current dipoles and minimum-norm current estimates ².

Results: The MMNm to words peaked 100-150 ms after the information in the acoustic input was sufficient for word recognition. At ~130 after the point in time when a word could first be recognized from the acoustic input, the left-superior-temporal generators of the MMNm showed their first activation peak, whereas those in left inferior-frontal areas did so with an additional delay of 22 ms ³. The latencies with which words were recognized corresponded to those of an MMN source in the left superior temporal cortex. There was a significant correlation ($r = 0.66$) of latency measures of word recognition in individual study participants with the latency of the activity peak of the superior temporal source.

Conclusions: The word recognition point of different words and of individual subjects was reflected in the peak latency of the left superior-temporal source of the MMNm, thus providing a tentative brain correlate of word recognition. The results are used to draw careful conclusions on the cortical organization and activity dynamics of cortical memory traces for words ⁴.

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Determinants Of Dominance: Is Language Laterality Explained By Physical Or Linguistic Features Of Speech? An MEG study.

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The laterality of language in the human brain is still not understood. Two main views are that the laterality is best explained (1) by left-cortical specialization for the processing of spectrally rich and rapidly changing sounds, and (2) by a predisposition of one hemisphere to develop a module for phonemes. We tested both of these views by investigating magnetic brain responses to the same brief acoustic stimulus, placed in contexts where it was perceived either as a noiseburst with no resemblance of speech, or as a native language sound being part of a meaningless pseudo-word. In further experiments, the same acoustic element was placed in the context of words. We found reliable left hemispheric dominance only when the sound was placed in word context. These results refute both main hypotheses of cortical laterality in showing that neither physical properties nor phoneme-status of a sound are sufficient for laterality. In order to elicit left-lateralized cortical activation in normal right-handed individuals, a rapidly changing spectrally rich sound with phoneme status needs to be placed in the context of frequently encountered language elements, such as words. This demonstrates that language laterality is bound to the processing of sounds as units of frequently occurring meaningful items and can thus be linked to the processes of memory trace formation for such items rather than their physical or phonological properties.

Time course of word meaning processing as revealed by magnetoencephalography

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Associative learning theory predicts that word form and semantics are tightly interwoven in the cortex. Action words referring to leg movements (e.g., “to kick”) should therefore activate cortical areas dorsal to those activated by words referring to actions performed with the upper body parts (“to eat”) ¹. In earlier studies, written action words activated different areas in the fronto-central cortex ²⁻⁴. Here, we look at spoken words and ask when the word-category-specific activity spreads toward fronto-central areas, and whether this differential activation is automatic and persists when subjects are instructed to ignore stimulus words and watch a silent video film.

Methods: 16 right-handed native speakers of Finnish heard the Finnish words “hotki” (to eat) and “potki” (to kick) presented as rare ($p=.17$) deviant stimuli in trains of frequent standard stimuli (SOA=1.4s). Standard stimuli were pseudowords (hotpi, potpi). 100-250ms after the critical stimulus divergence point (onset of second syllable), deviant stimuli elicited the magnetic Mismatch Negativity (MMNm) ⁵. To reveal the cortical sources of the MMNm, Minimum Current Estimates (MNCEs) ⁶ were performed on individual subjects’ data. ROIs for statistical analysis were defined so that they included superior temporal, inferior frontal, inferior central (face/hand) and superior central (leg) areas.

Results: MCEs indicated that in the left hemisphere the two words activated the four ROIs to different degrees; $F(3,45)=4.3$, $p<0.009$. Planned Comparison Tests confirmed stronger activation to “potki” than “hotki” in the leg ROI, $F(1,15)=23.8$, $p<0.0001$, whereas the inferior frontal and central ROIs revealed stronger activation to the face/arm word “hotki” compared with the leg word, $F(1,15)=8.0$, $p<0.005$. Time course analyses showed differences in the activation latencies of left hemispheric ROIs, $F(3,45)=4.8$, $p<0.003$. Superior temporal sources sparked at 160ms after the divergence point, followed by inferior frontal (172ms) and inferior central (arm) sources (176ms), $F(1,15)=3.9$, $p<0.03$, and, finally, the superior central (leg) ROI (200ms), $F(1,15)=17.1$, $p<0.0005$.

Conclusions: 150-200 after information about stimulus words is present in the input, a leg word activated leg areas in superior central motor and/or premotor cortex, and a face-/arm-related word such as “to eat” activated inferior frontal areas anterior to the motor cortex, probably in premotor and prefrontal areas. Aspects of word meaning are reflected in early quasi-automatic word-evoked cortical activity.

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Distinct effects of semantic plausibility and semantic structure building in MEG

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To date, research on the neurobiology of sentential semantic processing has focused almost entirely on the processing of semantic anomaly, which arguably only modulates processing at the lexico-semantic level, rather than tapping onto the combinatoric process of semantic structure building. In this study we used MEG to disentangle the effects of plausibility and semantic composition. To modulate semantic composition we employed complement coercion, i.e. expressions where event-selecting verbs such as 'begin', are combined with entity denoting objects (the professor began the book before his evening tea), in such a way that interpretation of the sentence requires creation of semantic structure that is not explicitly present in the input (e.g., the professor began [to read] the book). Extensive behavioral evidence suggests that complement coercions elicit processing delay (e.g. McElree, et al. Cognition, 2001). Coerced sentences were contrasted with implausible sentences violating verbal animacy restrictions (the professor disgusted the book before his evening tea), as well as plausible non-coerced control sentences (the professor read the book before his evening tea). Visual stimuli were presented to 16 healthy young participants while magnetic fields were recorded with a whole-head 148-channel MEG system. Multidipole modeling of activity elicited by implausible target nouns showed a classic N400 effect in the left temporal M350/N400m source (e.g., Helenius et al., Brain, 1998; Pykkänen & Marantz, TiCS, 2003). Coerced targets elicited no N400 effect, but were instead associated with larger amplitudes in an anterior midline source, which showed no sensitivity to semantic anomaly, and which peaked approximately 50ms after the M350/N400m. These results provide evidence against the hypothesis that the N400 effect is a reflex of semantic processing effort in any particularly linguistic sense. When semantic composition/integration is manipulated in well-formed plausible expressions, effects occur in the frontal lobe, not in the M350/N400m source.

MEG evidence for distinct processing of polysemy, homonymy and semantic relatedness bilaterally

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How are different senses of the same word represented (e.g., 'paper' meaning writing material and an article)? Are they represented in the lexicon or generated "on the fly"? Klein & Murphy (JML, 2001) found that activating one sense of a word slowed down processing of a different sense, concluding that senses were represented distinctly. Here we used magnetoencephalography to investigate whether sense-relatedness, i.e. polysemy, shows combined effects of phonological and semantic relatedness or whether polysemy effects are qualitatively different from the effects of sound and meaning relatedness alone, as predicted by theories where polysemy involves morphological identity. 17 healthy young participants judged whether visual two-word target phrases made sense, after judging a prime phrase involving either a homonym (savings BANK - river BANK), a polyseme (shredded PAPER - liberal PAPER) or a semantic relative (monthly magazine - shredded PAPER) of the target. Magnetic fields were recorded with a whole-head 148-channel MEG system and current sources modeled as equivalent current dipoles. Stimulus type affected source latency at 300-400ms bilaterally. In the left hemisphere, the latencies of the M350 source, hypothesized to index of lexical activation (e.g., Pykkänen & Marantz, TiCS, 2003) were reduced for polysemy and semantic relatedness, and delayed for homonym targets, as compared to unrelated controls. Concurrent activity in the right hemisphere showed a different pattern: source latencies were delayed for polysemy, reduced for semantic relatedness and showed no reliable effects of homonymy. These results suggest that polysemy processing is special: unlike homonym and semantic priming, polysemy priming involves parallel left-hemisphere identity priming of lexical activation and right-hemisphere competition between senses.

Changes in EEG Power Spectral Densities During Object Naming

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We examined power spectral density (PSD) changes in EEG data of nine adults during an object naming task. EEG data was acquired during the task using a net of 256 electrodes (Electrical Geodesics, Inc., Eugene, OR) in order to improve spatial resolution. All subjects had medically refractory left temporal lobe epilepsy and all were candidates for left temporal resection. This study was conducted prior to surgery. Results of preoperative intracarotid sodium amytal testing disclosed that essential language function was lateralized to the left side in all cases. The trials required each subject to provide the name of 80 common objects presented every 4 sec on slides. Each trial data consisted of 1 second before and 3 seconds after initial object presentation. The EEG data was analyzed in frequency bands of 25-30 Hz, 30-35 Hz, 35-40 Hz, 40-45 Hz, 45-50 Hz. The data were filtered in each band with a Remez band-pass filter. The PSDs for baseline and object-naming data were calculated after taking the Fourier transform of the data. The PSDs were averaged over 80 trials. Contour plots of the PSDs were constructed using a montage of the layout of the 256 channel electrode positions. The contour plots reveal that PSDs during object naming were 2-3 times higher than the baseline values for all frequency bands and with maximal changes lateralized to focal areas of the left cerebral hemisphere. These data suggest that it may be possible to noninvasively lateralize, and even eventually localize, cerebral regions essential for language.

Systematic cortical representation of vowel categories in the human auditory cortex

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This study aimed at determining how the human brain automatically processes phoneme categories irrespective of the large acoustic inter-speaker variability. Subjects were presented with 450 different speech stimuli, equally distributed across the [a], [i], and [u] vowel categories. A 306-channel magnetoencephalogram (MEG) was used to record N1m, the magnetic counterpart of the N1 component of auditory event-related potential (ERP). The N1m sources elicited by the vowel stimuli were estimated by means of sequential ECD fitting using a spherical head model. A 3-D reconstruction of the brain surface was used to determine the optimal individual location of the sphere.

The location of the N1m cortical sources were affected by the vowel category, the effect of which on the dipole locations was significant along the inferior-superior axis. The analysis of the N1m source strengths, Q, showed that the [i] stimuli having the largest F1-F2 distance evoked the strongest response, whereas the activation elicited by the stimuli from the [a] category exhibiting the smallest interformant distance had the smallest Q. This finding is interpreted in line with the vowel formant inhibition hypothesis [1]. We also found that the spectrum dissimilarities were reproduced in the cortical representations of the large set of the phonemes used in this study: vowels with similar spectral envelopes had closer cortical representations than those whose spectral differences were the largest. Our data further extend the notion of differential cortical representations in response to vowel categories, previously demonstrated by using only one or a few tokens representing each vowel category.

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Early Development of Neurophysiological Processes Involved in Normal Reading and Reading Disability

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This longitudinal study examined the development of brain mechanisms involved in phonological decoding in beginning readers using Magnetic Source Imaging. Kindergarten students were assigned to two groups: those who showed mastery of skills that are important predictors of proficient reading (Low Risk group--LR) and those who initially did not show mastery, but later benefited from systematic reading instruction and developed average-range reading skills at the end of Grade 1 (High Risk Responders--HR-R). Spatiotemporal profiles of brain activity were obtained during performance of letter-sound and pseudoword naming tasks before and after Grade 1 instruction. With few exceptions, LR children showed early development of brain activation profiles that are typical of older skilled readers. Provided that temporoparietal and visual association areas were recruited into the brain mechanism that supported reading, the majority of HR-R children benefited from systematic reading instruction and developed adequate reading abilities.

The English Irregular Past Tense: MEG evidence for morphological decomposition

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The lack of cross-modal priming from irregular verbs to their stems [1] has been used to support dual-route theories of inflection in which irregular past tense forms are memorized while regulars are compiled. Allen & Badecker [2] show that irregular past tense forms showing little orthographic overlap with their stems (*taught-teach*) do prime their stems. One interpretation of these results is that all irregular past tenses prime their stems, but that form overlap induces competition that cancels out the priming. Pykkänen & Marantz [3] review several MEG studies showing that the M350 (N400m) is sensitive to identity priming and morphological priming, but not to phonological competition. We use the materials of Allen & Badecker, but in a visual-visual priming paradigm. The M350 component is predicted to show priming effects for all categories of irregular verbs. We find that past tense forms prime their stems at the processing stage indexed by the M350, regardless of degree of form overlap. These results provide support for a decompositional analysis of the English irregular past tense.

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Neural Patterns of Semantic Interference During Reading Revealed by MEG

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Phonological and semantic processing are critical to fluent reading. Despite several neuroimaging studies localizing the cortical areas involved in these two processes, little is known about the interaction between them. Whole-head magnetoencephalography (MEG) was used to investigate the spatiotemporal pattern of cortical activity associated with the interaction between phonological and semantic processing during reading. Subjects had to judge whether two words, either homophone, synonym, or control pairs, sounded the same or different. The difference in the time taken to reject a synonym foil relative to a control foil, called the semantic interference effect (SIE), ranged from 20 to 30 ms. Two different analysis methods were applied to the data, Equivalent Current Dipoles (ECDs), and Minimum Norm Estimation (MNE). ECDs were fit sequentially to explain the magnetic field patterns of the control condition. To facilitate cross-condition comparisons, the same dipole locations and orientations were used to explain the magnetic field patterns of the synonym condition. In contrast to the 10-15 ECDs that were localized for each subject, the MNE solution estimated the source currents using a distributed approach. One aim of the present study was to compare the focal and distributed solutions in this task. ECD and MNE analyses revealed similar activation patterns, reflecting the congruence of the two approaches. Subjects exhibiting a robust SIE showed increased activation to the synonym relative to the control foils between 400 and 600 ms in areas known to be involved in semantic processing. However, for subjects who did not show the effect, the pattern appeared to be reversed across the two conditions.
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Time Course of Perisylvian Cortices Indicates Phonological Decoding Operations

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The process of translating print-to-sound, or grapheme-phoneme conversion, is normally referred to as phonological decoding. By definition, phonological decoding is required for reading aloud, but is less essential, or perhaps unnecessary for silent reading in skilled readers [1]. However, deficits in phonological decoding are commonly believed to form the basis of developmental dyslexia, as such impairments hinder children's ability to rapidly acquire new words. The current study investigates the spatiotemporal dynamics of phonological decoding operations in a group of skilled readers. To discern neural activity unique to phonological decoding processes, we acquired high-density magnetoencephalographic recordings during a multi-task paradigm utilizing a common stimulus set. Subjects viewed high-frequency concrete nouns, and were instructed to make surface-level judgments (i.e., font size) in task one and rhyme-judgments in task two. The raw recordings from each task were then transformed into brain activation profiles using standard dipole modeling techniques. Consistent with previous studies, concrete nouns evoked substantial activation in a distributed network of left hemisphere brain regions. In contrast to negligible neuroanatomical differences, the temporal dynamics of regional activation clearly distinguished the two tasks. In particular, neural activity unique to phonological decoding emerged ~450 msec after stimulus-onset, and was most prominent in left perisylvian cortices. We conclude left perisylvian neural regions mediate phonological processing, and activity specific to decoding operations commences late in the time course (~450 msec).

This work was supported in part by the MIND Institute.

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N400-like MEG Response Elicited by Verbs in English Relative Clauses

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Previous MEG studies have demonstrated an N400-like response elicited by semantically anomalous sentence-final words (e.g. Helenius et al., 1998; Halgren et al., 2002). In this study we extend these findings by showing that the N400-like response is elicited by sentence-medial verbs that mark the completion of a long-distance dependency in relative clause constructions. Comparison of the MEG responses elicited at multiple word positions shows that the N400-response reflects an enhancement of a response that is elicited in temporal cortex by all lexical categories in the sentence, but is selectively enhanced by the processing of semantic anomaly.

Subjects read sentences that were displayed word-by-word in a rapid serial visual presentation (RSVP) paradigm with a 500ms SOA. Sentences contained object relative clauses that were either congruous or incongruous at the verb position, e.g. “John prepared the sauce that the little girl happily {cooked, rolled} on the stove.” Incongruous conditions were created by crossing verb-noun combinations from pairs of congruous conditions, such that the nouns and verbs analyzed in the two experimental conditions were identical. Across two recording sessions, subjects read 200 instances of each condition interspersed with 400 filler sentences. MEG responses were recorded using a 160-channel array of axial gradiometers (KIT, Kanazawa, Japan). In 3 of 4 subjects analyzed to-date, results show a left-dominant temporal lobe source that is elicited around 400ms after both nouns and verbs alike. The field distribution of this response is consistent across recording sessions in the same subject. The response is selectively enhanced by presentation of a semantically anomalous verb. This N400-like response reflects the detection of semantic anomaly in the long-distance relation between the head of the relative clause and the embedded verb.

Separation of fetal and maternal magnetocardiographic signals in twin pregnancy using independent component analysis (ICA)

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ABSTRACT

The identification of fetal and maternal signals in magnetocardiograms (MCG) is central to data preprocessing and a prerequisite for data analysis and assessment. This is usually done by creating a template of the signal to be identified and marking data segments correlating to this template before averaging. This procedure is not only cumbersome, but may also lead to problems when there are several overlapping signals of interest such as in MCG recording in single or, more so, in twin pregnancy. Independent component analysis (ICA), which uses higher order statistics to decompose the signal into statistical independent components, has already been used in single pregnancies to distinguish between maternal and fetal signals. We applied the ICA algorithm TDSEP to 9 data sets of twin pregnancies acquired between the 28th and 38th week of pregnancy. Resulting ICA components can be used for further data analysis, e.g. for finding robust triggers or estimating the heart rate and its variability of the twins. The results showed that the maternal and fetal components can be separated from each other as well as from other sources of noise and artifacts. Differences between averaged ICA time curves and averaged raw data are not significant. Limitations include a concurrence of heart rates and changes in signal morphology due to gross movement. Nonetheless, ICA offers a fast and efficient approach for the preprocessing of MCGs with multiple signals of interest.

KEY WORDS: Magnetocardiography, fetal magnetocardiography, independent component analysis

INTRODUCTION

Recent progress in fetal magnetocardiography (FMCG) and magnetoencephalography (FMCG) has led to an increase in studies in this field. Central to both procedures is the identification of fetal and maternal signals in preprocessing and this is a prerequisite for data analysis and assessment of the signal of interest. The most commonly used method is based on the creation of a template of the signal to be identified and marking data segments correlating to this template before averaging. This procedure is cumbersome as, for each signal component to be processed, it requires visual inspection of the data and the manual selection of an appropriate number of data segments for a representative template. This is complicated when signals from several different sources are involved, such as in multiple pregnancy where the different cardiac sources often overlap. Furthermore, due to variation in signal shape (e.g. respiratory induced maternal QRS amplitude fluctuations or alterations in fetal MCG signal shape resulting from fetal movement), subtraction of the template will leave some residual signal. An alternative approach in the identification of signal sources is independent component analysis (ICA), which uses higher order statistics to decompose the signal into statistical independent components. This has already been used in single pregnancies to distinguish between maternal and fetal ECG signals [de Araujo, 2003, Vigneron 2003]. The aim of this work was to apply ICA to FMCG data, in particular those obtained in twin pregnancy, in order to examine the effectiveness of the method with respect to the standard approach.

METHODS

We studied 7 twin pairs between the 28th and 38th week of gestation. Data were obtained once in 6 pairs and 3 times in 1 pair for a total of 9 data sets. Different biomagnetometers were used to record FMCGs: 5 using a 37 channel system (Krenikon, Siemens, Erlangen) and 4 with a 61 channel biomagnetometer (Magne 1300C, 4D Neuroimaging, San Diego). For data acquisition the mothers were in a supine position with the biomagnetometer placed as close to the abdomen as possible. Data were usually recorded for 5 minutes at a sampling rate of 1 kHz and with a bandpass of 1-200 Hz. To reduce the effects of external noise, all measurements were performed in a standard shielded room (AK3b, Vacuumschmelze, Hanau).

Our standard procedure for identifying and separating the maternal and twin signals involves several steps (see also [van Leeuwen, 2004]). The maternal beats are identified on the basis of the correlation to a maternal QRS signal template and, at each beat, a signal averaged maternal PQRST trace is subtracted from the data set. In the resulting data, the cardiac signal of each of the fetuses is similarly and separately identified and the corresponding signal averaged PQRST traces are subtracted. This results in separate data sets, each containing primarily the cardiac signal components of only one of the subjects. Each set permits the examination of signal morphology, heart rate variability parameters and the duration of cardiac time intervals.

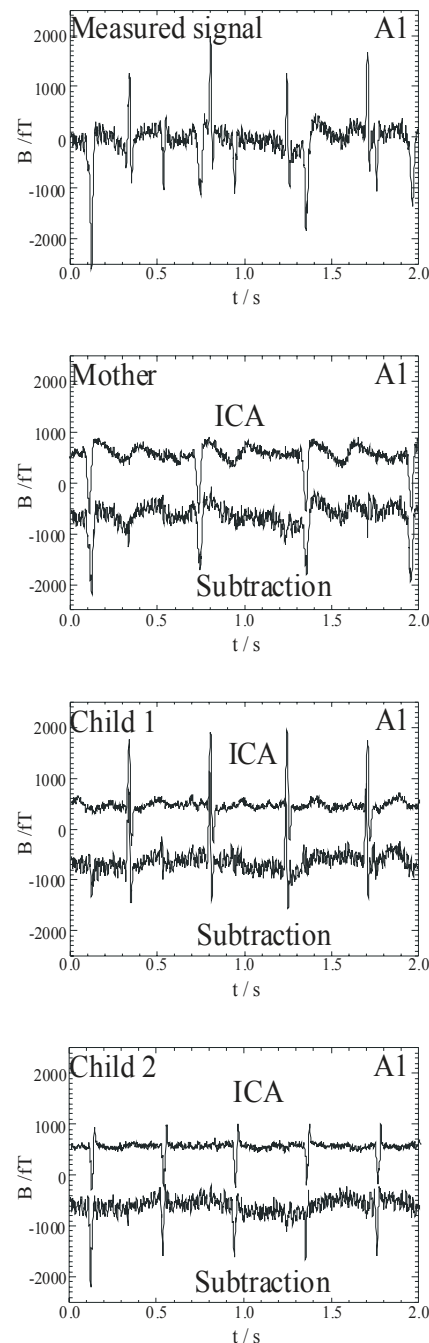


Figure 1. Measured and separated data in twin pregnancy are shown.

Each set permits the examination of signal

We applied ICA to separate fetal from maternal signals. The ICA model for stationary sources [Hyvärinen, 2001] to biomagnetic data assumes that the recorded data are a linear superposition of n sources of the form $f_i(t) = s_i(t) \cdot a_i$, where $s_i(t)$ is a time dependent amplitude function and a_i is a time independent field pattern in the m channel sensor system. This field patterns can be visualized as field maps of the sources. Combining the $s_i(t)$ into $s(t)$ and a_i into the matrix A , the vector $B_{meas}(t)$ of the time traces $B_{j,meas}(t)$ measured with the multi-channel sensor is given by:

$$B_{meas}(t) = A \cdot s(t) \quad (1)$$

The sources $s_i(t)$ and their maps a_i are unknown. ICA algorithms aim to calculate for the case $m = n$ the demixing matrix W^{-1} fulfilling:

$$W^{-1} B_{meas}(t) = u(t), \quad (2)$$

where the $u_i(t)$ are identical to the $s_i(t)$ if disregarding an indeterminacy in scale and ordering. ICA algorithms usually assume statistical independence between the sources, i.e. the joint probability density function of the signals $s_i(t)$ factorizes. Statistical independence can be tested by calculating the time-lagged cross-correlation $K_{ij}(\tau)$ between sources $s_i(t)$ and $s_j(t+\tau)$. Under the assumption of non-zero auto-correlations, statistical independence implies decorrelation for all time-lags $\tau > 0$, i.e. the time delayed correlation matrices are diagonal

$$\langle s_i(t) s_j(t+\tau) \rangle = K_{ij}(\tau) \delta_{ij}. \quad (3)$$

Equation (3) is the basis for the TDSEP algorithm [Bouchrani, 1997, Ziehe, 1998], which was applied to the fMCG signals.

RESULTS

The template method was successful in identifying practically all maternal heart beats. The method was highly successful with respect to the fetal beats acquired with the 61 channel system (8 data sets) and in those data sets acquired with the 37 channel system when the signal-to-noise ratio of the fetal QRS complex was high in at least one channel (5 data sets). In the remaining 5 data sets there were between 15-20% missed beats. After visual inspection and manual correction of missed beats and false marked signal artifacts, complete data sets could be created for all subjects. Using ICA it was possible to identify maternal heart beats in all recordings. The method was also highly successful with respect to the fetal beats in 7 of the 9 recordings. Only in 2 recordings ICA could not identify fetal beats due to ongoing movements.

Fig. 1 shows one typical channel of recorded signal and of separated maternal and fetal signals using both methods. In Fig. 2 the corresponding averaged signals are shown. It can be seen that averaged signals using ICA method are smoother than the averaged signals after subtraction method. A possible reason for this is that selected ICA components are not a complete description of the whole signal.

DISCUSSION

The template method for identifying magnetocardiographically recorded heart beats is dependable but can be cumbersome if the signal of interest is weak and difficult to identify with the naked eye. In such cases it requires time, experience and appropriate supplementary signal processing in order to find all beats.

In contrast, application of blind source separation requires no specific a priori knowledge in order to identify components generated from different sources. The method seemed to perform more efficiently; the more input channels were available. Resulting ICA components can be used for further data analysis, e.g. for finding robust triggers or estimating the heart rate and its variability of the twins. Limitations include a concurrence of heart rates and changes in signal morphology due to gross movement. Also the averaged signal may not contain all of the components which might be of importance in the assessment of waveform morphology.

Nonetheless, ICA offers a fast and efficient approach for the preprocessing of MCGs with multiple signals of interest, in particular when the signal-to-noise ratio is low.

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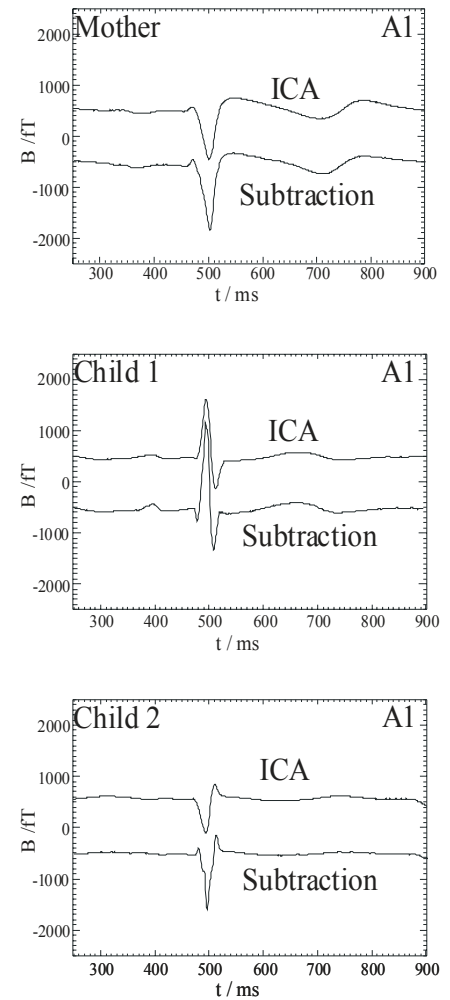


Figure 2. Averaged signals are shown of the mother, child 1 and child 2 using subtracted signals and ICA components.

Reconstruction of reliable fetal cardiac signals from fMCG recordings: comparison of methods

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ABSTRACT

The most common methods available in clinical practice for monitoring fetal cardiac activity during gestation do not allow the direct measurement of morphological and temporal parameters for fetal trace assessment [Peters, 2001]. Fetal Magnetocardiography (fMCG) obtained with super-conducting sensors positioned over the maternal abdomen inside a shielded room provide recordings that are contaminated by the maternal cardiac activity; consequently the maternal signal needs to be eliminated to reconstruct fetal cardiac signals. Aim of the present work was to compare two methods working in the time domain and used for fetal cardiac signals retrieval from fMCGs, an Independent Component Analysis algorithm (FastICA) and an Adaptive Maternal Beat Subtraction technique (AMBS). The detection rates of both methods were calculated; FastICA and AMBS performances were compared in the perspective of clinical applications by estimating several temporal and morphological characteristics of the retrieved fetal traces, such as P-QRS-T waves shape, noise reduction, arrhythmic beats detection. This direct comparison suggested that FastICA was superior to AMBS for clinical application of the recovered fetal signals.

KEY WORDS

Fetal magnetocardiography, ICA, signal processing techniques, prenatal diagnosis, electrophysiological measurements.

INTRODUCTION

Fetal Magnetocardiography (fMCG) is the non-invasive prenatal recording of magnetic field variations associated with cardiac electrical activity of the fetus above the maternal abdomen. The recorded traces are therefore a combination of signals produced by both the maternal and fetal hearts. As a result, the fetal signals must be separated from the maternal ones for a trustworthy employment of fMCG. Reliable signal processing techniques are necessary to achieve an accurate reconstruction of the time course of fetal cardiac activity for a quantitative assessment of cardiac temporal and morphological parameters. In this paper we compare two methods working in the time domain: 1) the Adaptive Maternal Beat Subtraction (AMBS), which is a deterministic technique normally used to recover fetal traces from fMCG by iteratively eliminating the average maternal signal; 2) the Fixed Point ICA algorithm (FastICA), which is based on the Independent Component Analysis (ICA) approach and has already been demonstrated to be an appropriate method for fMCG data processing [Comani, 2004]. The performances of FastICA and AMBS were compared with the respect to the characteristics of the reconstructed fetal signals, in the perspective of clinical applications.

METHODS

FMCG was performed by means of a flat 77-channel magnetometer, installed at the Institute of Advanced Biomedical Technologies (ITAB) of the Chieti University inside a magnetically shielded room to reduce the environmental magnetic noise [Della Penna, 2000]. Each channel consisted of a low-temperature dc-SQUID (Superconducting Quantum Interference Device) integrated magnetometer. All channels were kept at liquid helium temperature inside a cylindrical cryostat; 55 sensing magnetometers covered a circular area of 230 mm diameter, while the remaining 22 could be used for further noise reduction.

Eighteen pregnant women underwent recurring fMCG acquisitions every 3 to 4 weeks starting from about 22 weeks' gestation until delivery. A total of 51 fMCG data sets of 55 recordings each were available for the reconstruction of fetal signals in different gestational epochs. The MCG acquisition system was positioned over the fetal heart projection on the maternal abdomen as previously determined with an ultrasonographic exam, and fMCG signals were acquired for ten minutes with 1 kHz sampling frequency and a recording bandwidth between 0.016 Hz and 250 Hz. Maternal electrocardiogram (ECG) was simultaneously acquired with 3 amagnetic leads positioned on the maternal chest along orientations parallel to the X, Y, Z axes of the internal reference system of the MCG device.

The acquired fMCG data sets were processed in order to reconstruct the fetal traces using two different digital signal processing techniques: the Adaptive Maternal Beat Subtraction (AMBS) and the Independent Component Analysis (ICA). AMBS is a deterministic technique that can be used to remove artifacts with a known morphology, such as the maternal signal in the case of fMCG recordings, thus allowing the recovering of fetal signals [Abraham-Fuchs, 1990]. The average maternal beat can be defined, correlated to the original recording and subtracted with an iterative procedure, which is repeated for all 55 channels; depending on trace quality, a maximum number of 55 fetal signals is available for clinical analysis. On the other hand, ICA is a statistical technique that allows a blind sources separation starting from recordings containing mixed input signals, which should be independent from each other [Comon, 1994]. FMCG recordings satisfy this condition, since they result from the summation of the magnetic field variations associated to the electrophysiological activity of the maternal and fetal hearts, which, although producing similar signals, are independent from each other. The fundamental ICA constraint that the number of mixed traces must be greater than the number of independent sources is also met because the 55 simultaneous fMCG recordings available for ICA analysis were grouped in eight input clusters of 22 recordings each. Among the available ICA algorithms the Fixed Point ICA algorithm (FastICA) [Hyvärinen, 1999] was chosen for its computational efficiency. One raw fetal trace was retrieved from each cluster, and 8 simultaneous fetal signals were available for fetal cardiac activity analysis [Comani, 2004].

RESULTS

The efficiency of FastICA and AMBS was evaluated on all fMCGs; the comparison regarded morphological and temporal aspects of an electrophysiological cardiac trace, namely: 1) detecting fetal QRS complexes; 2) reconstructing fetal P-QRS-T waves preserving unmodified waveforms; 3) detecting fetal arrhythmias; 4) reducing all types of noise and increasing the SNR of reconstructed traces.

The rates of success of FastICA and AMBS in detecting fetal QRS complexes are given in Table 1 in function of gestational age. With

respect to the figures in the literature (80-85%), FastICA showed higher QRS detection rate (94%) while AMBS a lower one (67%). This outcome was even more marked when P and T waves detection was evaluated, with FastICA and AMBS scoring 90% and 37% respectively. Figure 1 gives an example of fetal trace reconstruction from raw fMCG. The maternal ECG is given in (a), fMCG in (b), and the fetal signals reconstructed from trace (b) with FastICA (c) and AMBS (d) are also shown. Several difficulties for the reconstruction of a reliable fetal trace were encountered in the presence of low SNR or fetal arrhythmias. Fetal extrasystolic beats were detected and correct QRS timing was retrieved by both methods, but FastICA also succeeded in restoring a trace of good quality, whereas traces obtained with AMBS were often affected by maternal interference and lower SNR.

DISCUSSION

The possibility of retrieving a consistent time course of fetal cardiac events prenatally and non-invasively is extremely valuable for a number of clinical applications. As regards the application of FastICA and AMBS to fMCG data, our results showed that both techniques were, in general, successful in reconstructing fetal cardiac signals, although their detection rates and performances were very different, especially with respect to the quality of the retrieved traces.

The detection rates obtained with FastICA were definitely better than the figures reported in the literature (80-85%), with an average score of 94% and a range between 80% and 100% from 22 weeks until end of pregnancy. Particularly remarkable are the figures obtained for early gestational epochs. On the contrary, AMBS was much less effective, with an average value of 67%.

As regards fetal arrhythmias, the effectiveness of FastICA was again extremely good (100%), and also AMBS performance was satisfactory (85%), although in many cases the traces reconstructed with AMBS were still strongly affected by several sources of noise, such as residual maternal signal, unclear P and T waves definition and overall low SNR.

In general, a large percentage of noise is still present in the fetal traces retrieved with AMBS, preventing a completely successful detection and characterization of fetal cardiac waves. On the other hand, FastICA separates noise sources as independent signal sources that may be disregarded in the process of fetal signals retrieval, with a consequent SNR increase in fetal traces with respect to original fMCGs.

It is evident from the above considerations that FastICA showed general better performances than AMBS. It is our opinion that FastICA should be preferred for the reconstruction of the time course of fetal cardiac signals in the perspective of clinical applications, being able to provide reliable traces in a variety of different initial conditions, such as early gestational epochs or extremely noisy input signals.

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	Gestational periods (weeks)				
	22 - 25	26 - 29	30 - 33	34 - 37	Total (22-37)
Available raw fMCG data sets	10	15	13	13	51
FastICA: QRS detection rate	8/10 (80%)	14/15 (93%)	13/13 (100%)	13/13 (100%)	48/51 (94%)
AMBS: QRS detection rate	3/10 (30%)	10/15 (67%)	10/13 (77%)	11/13 (85%)	34/51 (67%)
FastICA: P-QRS-T detection rate	7/10 (78%)	13/15 (85%)	13/13 (100%)	13/13 (100%)	46/51 (90%)
AMBS: P-QRS-T detection rate	0/10 (0%)	4/15 (27%)	6/13 (46%)	9/13 (69%)	19/51 (37%)

Table 1. FastICA and AMBS Detection rates expressed in function of gestational periods, given in weeks; values are given as the ratio between the number of reconstructed fetal traces and the number of available fMCG data sets; percent values are given in brackets.

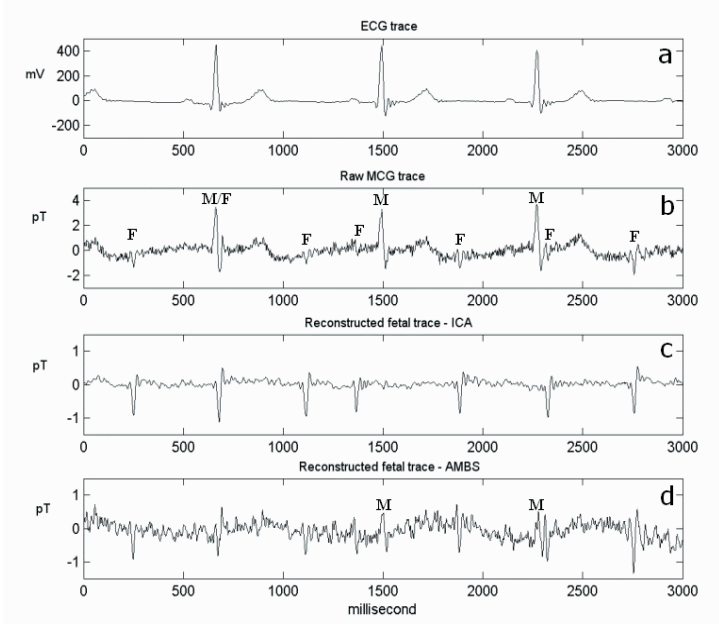


Figure 1. Example of fetal trace reconstruction from a fMCG recorded at 31 weeks' gestation; maternal and fetal QRS complexes are labeled with M and F respectively.

On-line Fetal Heart Rate Monitoring Using SQUID Sensor Arrays

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ABSTRACT

Objective: Fetal magnetoencephalography (fMEG) is the only complete non-invasive method to record fetal brain signals in the utero. When using this method in a clinical setting, it is necessary to monitor the fetal heart rate during the recordings. Based on the high sensitivity of the magnetic sensors used, it is not possible to record the heart rate simultaneously with fMEG by conventional methods like Doppler ultrasound. However, based on a large sensor array, the maternal and fetal magnetocardiographic signals (mMCG and fMCG) are recorded simultaneously with the fMEG with adequate temporal and spatial resolution. **Method:** Recordings were performed on a 151 channel SQUID array covering the whole maternal abdomen (SARA system). We use a multichannel adaptive filter to cancel the maternal signal and dynamically select those channels with high content of fetal signal. Our technique can be implemented in real time using a recursive steepest descent algorithm. From the extracted fMCG signal, we obtain an on-line estimate of the heart rate with an R-wave detector that uses a smoothed first derivative magnitude of the signal. **Results:** We show through real data that, with this technique, we obtain real-time estimates of the fetal heart rate with a small standard deviation. Furthermore, our proposed criterion for channel selection can identify the channels with low or high content of fetal signal. **Conclusion:** We developed a fast and reliable fMCG extraction method, which has on-line capability. Currently, initial studies are conducted with an experimental setup, allowing the on-line access to the magnetic signals of all 151 channels. Our method will help to establish fetal magnetometry in a clinical setting, where continuous control of vital signals of the fetus is necessary.

KEYWORDS

Fetal magnetoencephalography, magnetocardiography, adaptive filtering, signal cancellation.

INTRODUCTION

Fetal magnetoencephalography (fMEG) is a completely passive and non-invasive technique for the study of fetal brain function *in utero* [Lenge, 2001]. fMEG is measured in the presence of environmental noise and various near-field biological signals: maternal magnetocardiogram (mMCG), fetal magnetocardiogram (fMCG) uterine smooth muscle (magnetomyogram), and motion artifacts [Wakai, 2002]. In clinical studies, it is necessary to monitor the fetal heart rate during the recordings. However, traditional techniques such as fetal electrocardiogram (fECG), uterine pressure sensors, or Doppler ultrasound, do not provide with complete information of the cardiac function.

fMCG has multiple advantages for the analysis of the morphology and temporal parameters of the fetal heart signals [Lewis, 2003]. It fills the diagnostic gap left by the difficulties involved in recording fECG due to the insulating effect of the *vernix caseosa* and the existence of preferred conduction pathways between the fetal heart and maternal abdomen. Furthermore, fMCG is detected as early as the 16th week of gestation, and measurements can be obtained simultaneously with fMEG using a sufficiently large sensor array and adequate sample rate.

However, the detection of the fMCG signal depends on the ability to separate the fetal heart component from the composite signal. In general, the mMCG and fMCG signals are the dominant components of the ensemble, with an average magnitude as large as 10 pT at the fetal thorax location. Closer to the maternal heart, the mMCG can be as large as 100pT [Vrba, 2003]. Therefore, algorithms for heart rate monitoring based on MCG have to overcome not only this problem, but need to have a low computational complexity and low processing delay, and must be able to detect rapid and dramatic changes in the heartbeats in a beat-to-beat manner.

In this paper, we present an algorithm based in a multichannel filter to adaptively separate the fMCG signal from the mMCG, as well as dynamically select those channels with highest content of fetal signal and monitor the fetal heart activity on-line.

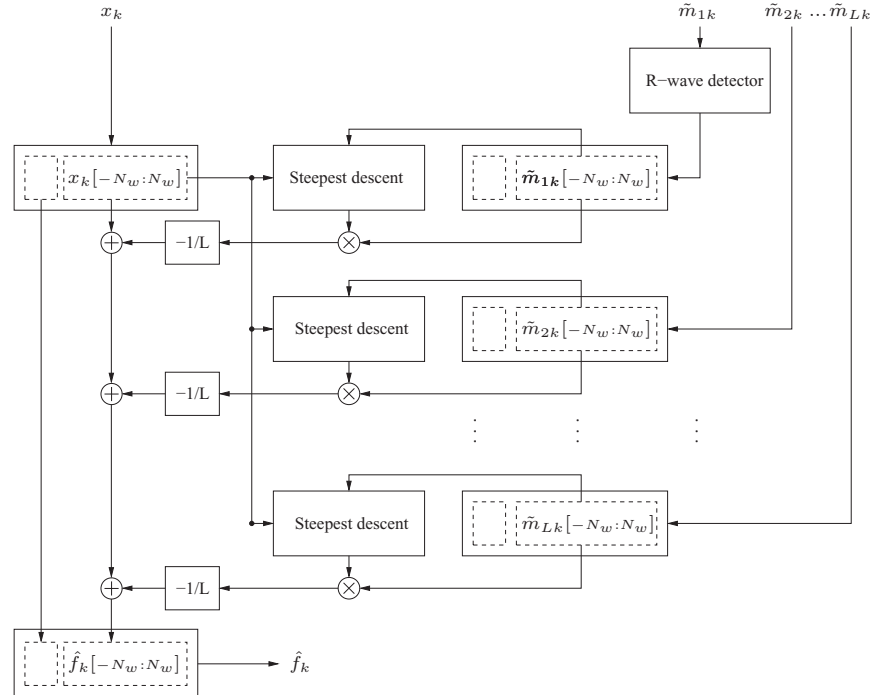


Figure 1: Diagram of the multichannel adaptive filter.

METHODS

We define our measurement model as $x(n) = f(n) + m(n)$, where $x(n)$ is the measurement of a single channel, $f(n)$ is the fetal signal component, $m(n)$ is the maternal signal component plus noise, and $n = 1, 2, \dots, N$ time samples. Our goal is then to cancel $m(n)$ from $x(n)$. This problem can

be seen from the point of view of adaptive signal processing as a case of *signal cancellation* [Hayes, 1996] in which the process $f(n)$ is to be estimated from a corrupted observation $x(n)$.

Consider that a group of L channels can be used as *reference*, i.e. they contain mostly maternal signal. Refer to each of the reference measurements as $\tilde{m}_i(n)$, where $i = 1, 2, \dots, L$. Although $\tilde{m}_i(n)$ will be correlated with $m(n)$, the two processes will not be equal. Therefore, it is not possible to estimate $f(n)$ simply by subtracting $\tilde{m}_i(n)$ from $x(n)$. Instead, we use an adaptive filter to estimate $m(n)$ and then subtract it from $x(n)$, i.e. $\hat{f}(n) = x(n) - \hat{m}(n)$, where $\hat{f}(n)$ and $\hat{m}(n)$ are the estimates of the fetal and maternal signals, respectively, at the n th time sample. If we assume that we can temporarily store N_T time samples of our on-line measurements in a buffer, then we can define $\mathbf{x}_k = [x(n_0), x(n_0 + 1), x(n_0 + 2), \dots, x(n_0 + N_T - 1)]^T$, and $\tilde{\mathbf{m}}_{ik} = [\tilde{m}_i(n_0), \tilde{m}_i(n_0 + 1), \tilde{m}_i(n_0 + 2), \dots, \tilde{m}_i(n_0 + N_T - 1)]^T$, where n_0 is an arbitrary starting time sample such that $n_0 + N_T - 1 \leq N$ at the k th buffer stored. Now, the estimate of the maternal signal at the k th buffer is given by $\hat{\mathbf{m}}_k = (1/L) \sum_i w_{ik} \tilde{\mathbf{m}}_{ik}$, where w_{ik} is the adaptive coefficient corresponding to the i th reference signal. We use the *steepest descent* algorithm to compute the adaptive coefficients recursively while keeping the mean square error of $\hat{\mathbf{f}}_k$ minimized. According to this algorithm, our adaptive coefficients are given by $w_{i,k+1} = (1 + \mu \hat{\sigma}_{\tilde{\mathbf{m}}}^2) w_{ik} + \mu \hat{\sigma}_{\mathbf{x}\tilde{\mathbf{m}}}^2$, where μ is the step size, $\hat{\sigma}_{\tilde{\mathbf{m}}}^2$ is the sample variance of $\tilde{\mathbf{m}}_{ik}$, and $\hat{\sigma}_{\mathbf{x}\tilde{\mathbf{m}}}^2$ is the sample covariance between $\mathbf{x}_k$ and $\tilde{\mathbf{m}}_{ik}$.

Accurate on-line removal of the maternal signal requires all calculations to be done in synchrony with the peak produced by the maternal heart beat. The detection of this peak is achieved through an R-wave detector that uses a smoothed first derivative of the signal [Köhler, 2002], i.e. $\Theta = 0.4 \max\{[0.25, 0.5, 0.25]^T * |\tilde{\mathbf{m}}'_{1k}|\}$, where Θ is the threshold of the detector, and $\tilde{\mathbf{m}}'_{1k}$ is the first derivative of $\tilde{\mathbf{m}}_{1k}$. Note that only the first of the reference channels is passed through the R-wave detector as we consider that the delay between the reference signals is negligible. Once we have detected the peak of the maternal signal, all computations are done for windows of $2N_w + 1$ time samples from both $\mathbf{x}_k$ and $\tilde{\mathbf{m}}_{ik}$: N_w samples before and N_w after the peak, where N_w is the window size.

Finally, the estimate of the fetal signal at the k th iteration is obtained as $\hat{\mathbf{f}}_k = \mathbf{x}_k - \hat{\mathbf{m}}_k$. A complete diagram of our adaptive filter is shown in Fig. 1. Further details of our method can be found at <http://cyclone.ece.uic.edu/~david/onlinefHRM>.

EXAMPLE

We applied our adaptive filter to real magnetic data from a 151 channel SQUID array covering the whole maternal abdomen (CTF SARA system). Our data was sampled at 312.5 Hz and then low-pass filtered at a cut-off frequency of 40 Hz. The 7 upper rim channels were used as our reference channels $\tilde{m}_i(n)$, i.e. $L = 7$. We considered a buffer size $N_T = 300$ and a window size $N_w = 80$. These values were chosen accordingly to the Nyquist rate. For the steepest descent algorithm, we chose a step size $\mu = 0.1$.

Our preliminary results showed that $|w_{ik}| \rightarrow \mu$ for those channels with high content of fetal signal. Using this criterion, we chose the signal from one of these channels to estimate the heart rate. This estimate was obtained at each window through an R-wave to detect the peaks of the estimated fetal signal $\hat{\mathbf{f}}_k$. Such R-wave detector was implemented in the same way as explained in the previous section. A snapshot of $\mathbf{x}_k$ and $\hat{\mathbf{f}}_k$ for the selected channel, as well as the estimated fetal heart rate, are shown in Fig. 2.

CONCLUDING REMARKS

We have presented a reliable and fast method with on-line capabilities to extract the fMCG signal. Our method is based in an adaptive filter to cancel the maternal signal component. This technique also allowed us to identify those channels with poor, regular, or high content of fetal signal by keeping track of the values of the adaptive coefficients. This capability may be also used to track on-line changes of the fetus position and allow adaptive channel selection. Finally, using this procedure for a specific channel, we can obtain an accurate estimate of the fetal heart rate. Our method will help to establish fetal magnetometry in a clinical setting, where continuous control of vital signals of the fetus is necessary.

ACKNOWLEDGMENT

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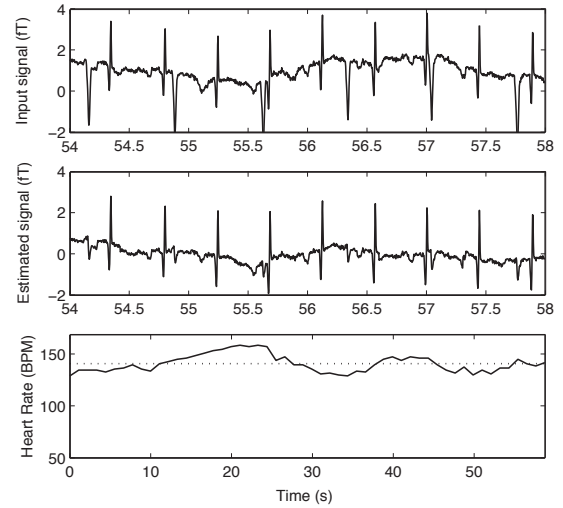


Figure 2: From top to bottom: Input signal ($\mathbf{x}_k$), output signal ($\hat{\mathbf{f}}_k$), and estimate of the fetal heart rate (mean shown in dotted line).

A vector magnetometer for standardization of fetal magnetocardiogram waveforms and analysis of fetal arrhythmias

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ABSTRACT

Although fetal magnetocardiography (fMCG) has been recognized as a useful technology for analysis of fetal cardiac events in the last decade, fetal orientation and movement affects the fMCG waveform, making it difficult to standardize the waveform. The aim of this study was to investigate the usefulness of vector magnetometers for compensation of these limitations. We studied 73 fetuses (gestational age, 22-40 weeks), 41 without and 32 with fetal or maternal complications. fMCG was recorded twice in each case and the two waveforms were compared to investigate the effects of fetal orientation. The SQUID system used in this study was a 12-channel vector magnetometer (Hitachi), by which the three components of the magnetic field (Bx, By, Bz) can be detected at four measurement points. By constructing the three components, a composite waveform (Bxyz) was obtained. The success rate of recording was 100% for QRS waveform and those for p and T waves after signal averaging were 97 and 78%, respectively. The polarity of the composite waveforms was always positive, independent of fetal orientation and movement, and the time resolution was high. Even before signal averaging, waveforms with high time resolution were recorded in at least one of the three components, making it possible to more precisely analyze fetal arrhythmias including supraventricular tachycardia and atrioventricular block. Vector magnetocardiography can be used to standardize the fMCG waveform and to provide a more complete and accurate reading in the fetus.

KEY WORDS

Cardiac time interval, fetal magnetocardiography, fetal arrhythmia, vector magnetometer

INTRODUCTION

Recent advances in the technology of superconduction quantum interference device (SQUID) magnetometers has made it possible to record and study extremely weak magnetic signals from the fetal heart. Lately, there has been particular interest in the study of electric activity of the fetal heart using fMCG [Horigome, 2001] [Menedez, 2001] [van Leeuwen, 2004] [Wakai, 2003]. Since fMCG provides detailed diagnosis of fetal arrhythmias, it is logical to administer antiarrhythmic agents transplacentally based on accurate diagnosis [Fouron, 2003] [Menedez, 2001] [Wakai, 2003]. However, the fMCG waveforms tend to be largely affected by fetal orientation and movement, making it difficult to compare the waveforms among fetuses in various positions. The fMCG waveforms even fluctuate during measurement in the same fetus. Furthermore, fMCG data somewhat vary depending on the SQUID system used and the protocol of data acquisition [Stinstra, 2002]. Recently, an international protocol was provided on trial to establish standard methods for acquiring and analyzing fMCG data [Grimm, 2003]. The aim of this study was to investigate the usefulness of vector magnetometers for compensation of these limitations.

METHODS

We studied 73 fetuses (gestational age, 22-40 weeks, median, 32), including 41 without and 32 with fetal or maternal complications, including fetal arrhythmia (10 cases), intrauterine growth retardation (11 cases), various congenital anomalies (7 cases) and maternal disease such as toxemia (4 cases). The SQUID system used in this study was a 12-channel vector magnetometer (Hitachi) housed in a magnetically shielded room at the University Hospital of Tsukuba. Using this SQUID system, three components of the magnetic field (Bx, By, Bz) can be detected simultaneously at four measurement points. By constructing three components according to the method described in our previous report, a composite waveform (Bxyz) was obtained [Kandori, 1999]. fMCG was recorded twice in each case and the two waveforms were compared with each other to investigate the effect of fetal orientation. The success rate of recording P, QRS, and T waves for each component (Bx, By, Bz) and after composition (Bxyz) was assessed. We also assessed those of p and T waves after signal averaging triggered by the QRS peak. The values of PR, QRS and QT intervals were obtained after signal averaging, and correlations of those intervals with the gestational age were investigated. Fetal arrhythmias were analyzed without signal averaging of the waveform with the highest spatio-temporal resolution among 12 channels.

RESULTS

The detection rate before signal averaging for QRS was 100%, and that for P and T waves ranged from 74 to 94 and from 53 to 75% among the three components, respectively. The most frequently detectable component was Bz. After signal averaging, the detection rate for p and T waves increased to 97 and 78%, respectively. Due to the low amplitude nature of the T wave in the fetus, approximately 25% of the subjects showed ambiguous onset or end of the point for T waves even though a T wave appeared, and those cases were excluded from further analysis. The detection rates for P and T waves varied significantly with gestational age and depth of the fetal heart.

By constructing the three components of the magnetic fields (Bx, By, Bz), high time resolution PQRST waveforms were obtained. The composite waveforms showed similar pattern among normal fetuses, always with positive polarity. The QRS intervals in normal fetuses ranged from 51 to 85 msec (64 ± 6 , mean $\pm$ SD), and correlated with gestational age. The PR interval (97 ± 14 msec) and QT interval (248 ± 13 msec) were rather of constant values during the period of concern. QRS waveforms with abnormal shape and prolonged duration were recognized in the fetuses with myocardial hypertrophy. Examples of the composite waveform in a normal fetus and a fetus with myocardial hypertrophy are presented in Figs. 1 and 2, respectively.

Fetal arrhythmias were analyzed on a tracing with the best spatio-temporal resolution and the highest amplitude among 12 channels before composing three magnetic components. Typically, the resolution of at least one of the tracings was satisfactory for analysis. Detailed investigation of fetal arrhythmia was possible. The waveforms of supraventricular tachycardia and congenital heart block are presented in Figs. 3 and 4, respectively.

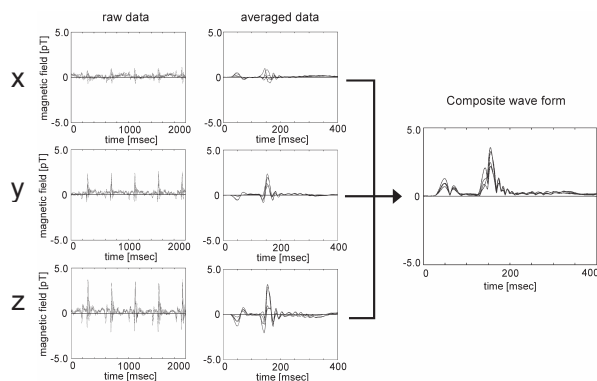


Figure 1. Vector magnetocardiograms in a normal fetus. Vector magnetometer before (left) and after (right) signal averaging. Construction of the three components (X, Y, Z) of the magnetic fields results in more distinct waveforms with high time resolution.

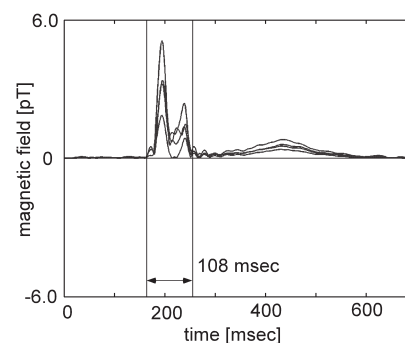


Figure 2. Vector magnetocardiogram in a fetus with ventricular hypertrophy. Note the abnormal QRS waveform with prolonged duration.

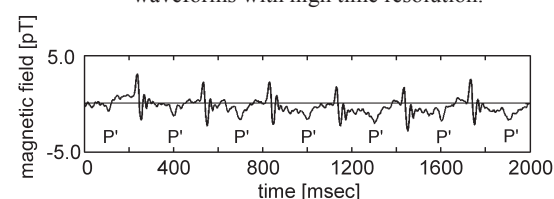


Figure 3. Magnetocardiogram of fetal tachycardia. The type of tachycardia is determined as long R-P' supraventricular tachycardia.

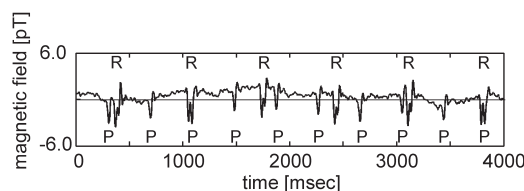


Figure 4. Vector magnetocardiograms of fetal bradycardia. Complete atrioventricular block is demonstrated.

DISCUSSION

The fetal PQRST waveforms obtained by vector magnetometer were similar among normal fetuses. Those recorded twice at different intervals also tended to show similar configuration in each case independent of fetal position or orientation. These results suggest that the vector fMCG would be useful for standardization of the fMCG waveform and to establish the normal values of fetal cardiac time intervals. In the present study, the success rates of detection of QRS and P waves were satisfactory. However, that for the T wave was rather low, as higher detection rate for T wave, over than 90%, has recently been reported using conventional SQUID magnetometer [Grimm, 2003] [van Leeuwen, 2004]. This is partly because we excluded cases with ambiguous onset or endpoint of T wave as unsuccessful. In the subjects that we considered successful in detecting T waves, the time resolution was improved by constructing a composite waveform. For analysis of fetal arrhythmias, in which analysis on a raw tracing is necessary, vector magnetometer was also useful, because at least one component of the vector magnetocardiogram showed efficient spatio-temporal resolution regardless of fetal orientation or movement during measurement, and we could select the best tracing for analysis. In conclusion, vector fMCG seems to provide a complete and accurate reading as well as a standard waveform in the fetus. Thus, it is possible that after introduction of standard methodology, the fMCG becomes acceptable as a reliable diagnostic tool in perinatal medicine [Grimm, 2003].

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Magnetocardiography in Fetuses with Congenital Structural Heart Diseases

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ABSTRACT

Fetal magnetocardiography (FMCG) has been applied to various fetal diseases. However, the application of FMCG to fetal structural heart anomalies has rarely been reported. The purpose of this study was to investigate the clinical usefulness of FMCG in the prenatal diagnosis of fetal structural heart diseases. Fourteen fetuses, including three with a single ventricle and two with transposition of the great arteries, were included in this study. Diagnoses were made prenatally by fetal echocardiography and were confirmed after birth. FMCG was recorded between the 31st and 40th weeks of gestation using a 64-channel SQUID system (MC-6400, Hitachi, Japan) after fully informed written consent. The average FMCG was generated from 100 cardiac cycles triggering R peaks after removing the maternal FMCG signals. The intervals of each PQRST were measured. Current-arrow maps were useful for determining the starting points and end-points of each component. QTc was calculated from QT- and RR-intervals. QTc intervals were prolonged more than 450 ms in 7 fetuses, 6 of which died in the early neonatal period. These results imply that FMCG may be useful for fetal QT prolongation, which might be related to neonatal poor prognosis.

KEY WORDS

magnetocardiogram, fetus, neonate, structural heart disease, QT interval, QT prolongation, prognosis

INTRODUCTION

Recent improvements to magnetocardiography allow the measurement of magnetic fields as faint as a fetal heart. This increased sensitivity is due to improvement of the superconducting quantum interference device (SQUID), and a measurement system of 64 channels for magnetocardiography is now commercially available in Japan (MC-6400, Hitachi Ltd.). It has previously been difficult to record fetal electrocardiograms in utero as the fetal skin is entirely covered by the caseous vernix until late gestation. Since magnetic flux can pass through the caseous vernix, the magnetic field generated by a fetal heart can be recorded without remarkable attenuation. Fetal magnetocardiography (FMCG) has therefore been applied to various fetal diseases such as arrhythmia [Wakai, 1998] [Hosono 2001a] [Hosono 2002b] [Hosono 2002c] [Hosono 2002d], cardiac hypertrophy [Horigome 2001] and variability change of fetal heart rate [Van Leeuwen 1999]. However, the application of FMCG to fetal structural heart anomalies has rarely been reported. The purpose of this study was to investigate the clinical usefulness of FMCG in the prenatal diagnosis of fetal structural heart diseases.

METHODS

This study was approved by the local ethics committee. Fourteen fetuses were included in this study. All patients were referred to the National Cardiovascular Center, Osaka, Japan for suspected fetal congenital structural heart diseases. The diagnoses were made prenatally and were confirmed after birth. The neonates were taken care of by specialists in neonatal cardiology in the National Cardiovascular Center.

A 64-channel SQUID system (MC6400) installed in the National Cardiovascular Center was used for all measurements. FMCG was recorded for 2 min between 31 and 40 weeks' gestation. The raw data were stored in a computer, and after filtering and removing maternal MCG signals, the average FMCG triggered at R peaks was calculated for 100 beats. We measured P-, T-, QRS- durations, and PR- and QT-intervals in the averaged FMCG. Current-arrows maps were helpful for determining the durations and intervals. QTc was calculated from QT using R-R interval. The normal values for unaffected fetuses were referred to the data of normal Japanese fetuses [Horigome 2000].

RESULT

Fetal MCG was successfully recorded in all cases. Although P- and T- durations and PR intervals were within the normal limits in all cases (Fig.1 for PR-intervals), QRS durations exceeded the normal limit in 3 cases. QTc was longer than the normal limit in 7 cases (Fig.2). Six of the 7 cases with structural heart disease and prolonged QTc died within 28 days after birth in spite of intensive neonatal care.

DISCUSSION

In previous studies of MCG findings of congenital structural heart diseases, only a few cases of heart disease without serious complications such as ventricular septal defect and atrial septal defect were reported [Horigome 2001] [Kahler 2002]. As the majority of fetuses with heart disease in western Japan are referred to the National Cardiovascular Center, most fetuses with severe heart diseases could be included in this study. The QT prolongation of congenital long QT syndrome has been revealed by several authors using MCG [Hamada 1999] [Menendez 2000] [Kandori 2001] [Hosono 2002a]. QT prolongation of congenital atrioventricular heart block was also reported [Hosono 2002d]. Diseases with QT prolongation had rather high mortality because QT prolongation relates to the abnormal contractility of ventricular muscles. QT prolongation of congenital heart diseases may be related to the prognosis of neonates, and thus MCG may be a good predictor of neonatal prognosis.

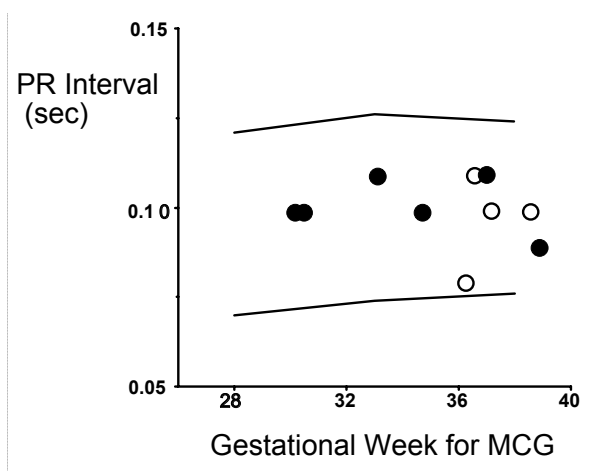


Figure 1. PR intervals measured by magnetocardiography in fetuses with congenital structural heart diseases. Open circles. Fetuses survived more than 28 days after birth. Closed circles. Fetuses died within 28 days after birth. Lines. Normal limits for Japanese fetuses without heart diseases.

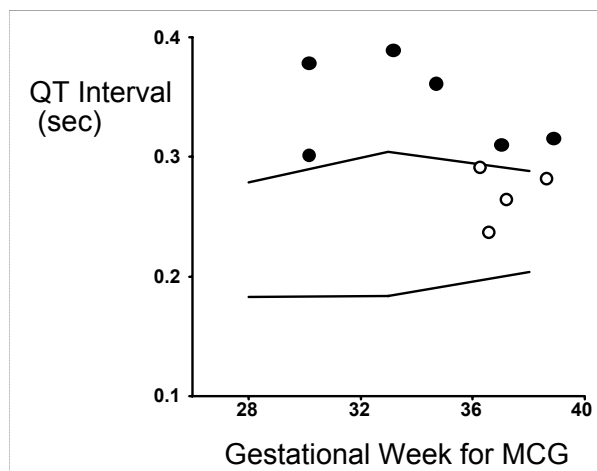


Figure 2. QT intervals measured by magnetocardiography in fetuses with congenital structural heart diseases. Open circles. Fetuses survived more than 28 days after birth. Closed circles. Fetuses died within 28 days after birth. Lines. Normal limits for Japanese fetuses without heart diseases.

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Autocorrelation detection of R-wave peak in fetal magnetocardiogram

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ABSTRACT

We have developed a new diagnostic method of detecting an R-wave peak simply and correctly using a fetal magnetocardiogram (FMCG) signal to obtain RR interval trend. The method uses an autocorrelation function of a raw data and fetal template waveform. After calculating the autocorrelation function, we detected the peak time as a fetal heart beat. This method could provide a simple method for detecting an accurate fetal heartbeat.

KEY WORDS

Magnetocardiogram, autocorrelation, R-R interval

INTRODUCTION

Fetal magnetocardiogram (FMCG) signals, which were first measured by Kariniemi et al in 1974, have been used to diagnose fetal heart disease because there is little interference from the maternal MCG and the vernix caseosa. Many researchers have studied power spectral analysis [Rassi 1995] [Kandori 1998] [Kotini 2001] and heart rate variability [Kariniemi 1977] [van Leeuwen 1999]. Recently, supraventricular tachycardia has been determined using a rhythm pattern [Wakai 2003]. In the present paper, we introduce an automatic method for detecting R-R interval using FMCG [Kandori 2003].

METHODS

The data flow of detecting an R-R interval is shown in Fig.1. The thin boxes indicate a process and bold boxes indicate obtained data. To remove low-frequency noise (maternal breath or fetal moving noise), a band-pass filter (5-50 Hz) is first applied to a raw FMCG signal. After filtering, a template waveform of the maternal MCG at each channel is made. The maternal MCG template was averaged 20-30 times by using an R-wave peak of the ECG as a trigger. So as not to create a discontinuous raw waveform, the baseline in each template from the beginning point to the end of the template must be adjusted mathematically so that the baseline is zero. Using the maternal MCG template with the adjusted baseline, each maternal MCG signal is removed from the raw signal on each FMCG signal. These processes make it possible to obtain a clear FMCG raw signal. After removing the maternal MCG signals, averaged FMCG template QRS waveforms are produced using the raw signal. The averaging process is performed manually to obtain a correct QRS complex waveform.

RESULTS

The autocorrelation function of each channel can be calculated. Therefore, to obtain a clear autocorrelation function, five channels' autocorrelation functions were averaged. The averaged function is shown in middle figure of Fig. 2, where the clear peak can be seen. Peak time was detected using a threshold of 0.6 and the results are indicated as a circle in lower figure of Fig. 2.

DISCUSSION

It can be considered that R-R interval variability reflects fetal autonomous nervous system or neurological development. Therefore, it is necessary to detect R-wave peak correctly. This method of detecting an R-R-interval using autocorrelation of FMCG signals has the ability to obtain the R-R-interval trend simply and correctly.

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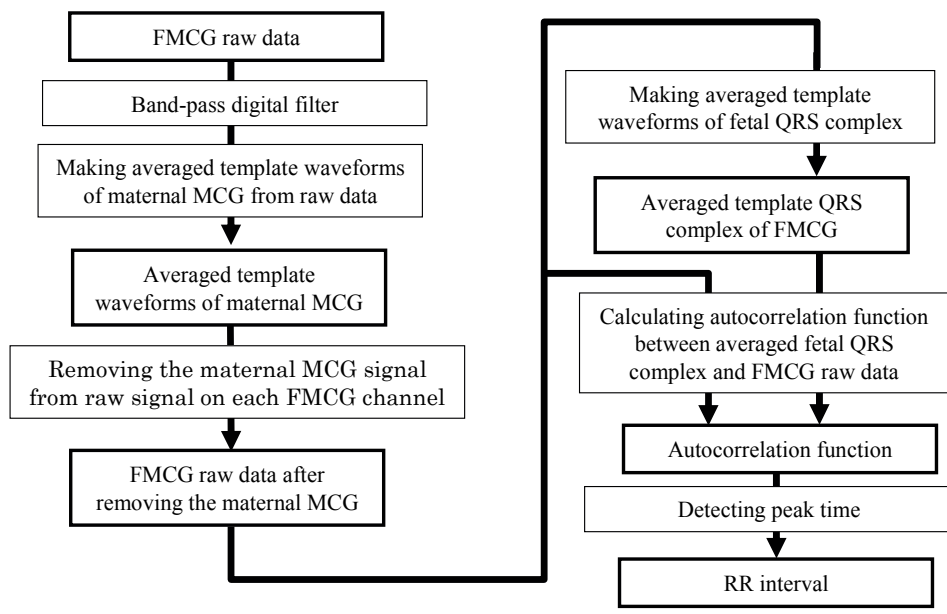


Fig. 1 Data processing for detecting R-R interval.

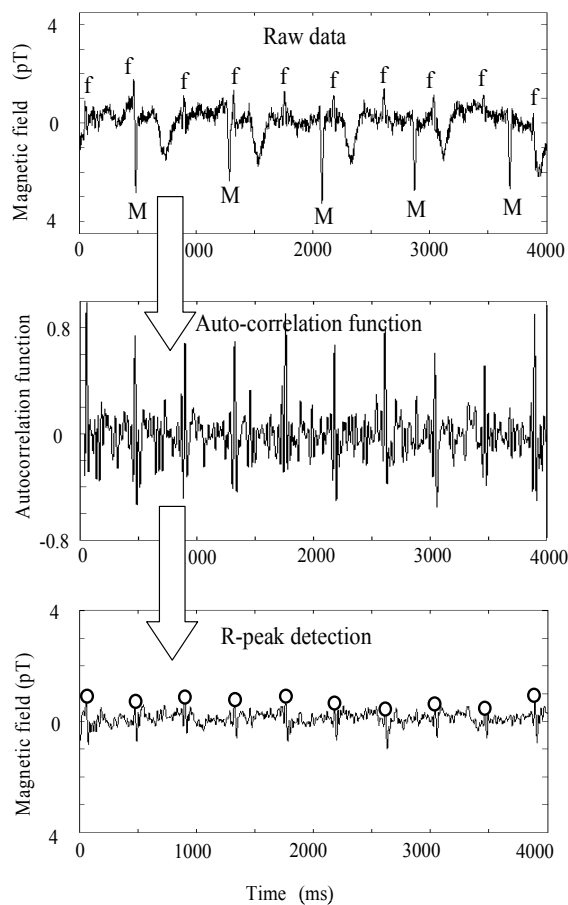


Fig. 2 Results for R-peak detection

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HTS Magnetometers for Fetal Magnetocardiography

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ABSTRACT

High temperature superconducting (HTS) SQUID sensors have adequate magnetic field sensitivity for adult magnetocardiography (MCG) measurements, but it remains to be seen how well they perform for fetal MCG (fMCG), where the heart signals are typically ten times smaller than the adult signals. In this study, we assess the performance of a prototype HTS SQUID system; namely, a three-SQUID gradiometer formed from three vertically-aligned HTS dc-SQUID magnetometers integrated into a fiberglass liquid nitrogen dewar of diameter 12.5 cm and height 30 cm. Axial gradiometers with short or long baseline, as well as a second order gradiometer, can be formed out of these magnetometers via electronic subtraction. The calibrated magnetometer sensitivities at 1kHz are 109 fT/(Hz)^{1/2}, 155 fT/(Hz)^{1/2} and 51 fT/(Hz)^{1/2}. Direct comparison is made between the HTS SQUID system and a LTS SQUID system by making recordings with both systems during the same session on adult and fetal subjects. Although the fMCG could be resolved with the HTS SQUID system in most near-term subjects, the signal-to-noise ratio was relatively low and the system could not be operated outside of a shielded room.

KEY WORDS

fetal magnetocardiography, high temperature superconductor, superconducting quantum interference device

INTRODUCTION

The first fMCG studies were performed in 1974 [Kariniemi, 1974]. Since then, a number of investigators have demonstrated the value of the diagnostic information provided by fMCG, especially for evaluation of fetal arrhythmia [e.g. Van Leeuwen, 1999; Wakai, 2003]. However, clinical utilization of this technique has been limited by the high cost and high maintenance associated with low temperature superconductor (LTS) SQUID systems, as well as the need for magnetic shielding. The breakthrough of high temperature superconductor (HTS) SQUID technology potentially will allow resolution of several fT/(Hz)^{1/2} to be achieved at liquid nitrogen temperatures, and has motivated such projects as FHARMON [ter Brake, 2002], which have investigated the feasibility of HTS SQUID systems for fMCG. In this study we compare the performance of a HTS system with a LTS system for measurement of adult and fetal MCG.

METHODS

We assembled and evaluated a prototype HTS SQUID system, which utilized yttrium barium copper oxide (YBCO) SQUID sensors in a flip-chip configuration, produced by Faley and coworkers [Faley, 2001, 2002]. The system was configured as a three-SQUID gradiometer, consisting of three vertically aligned magnetometers with 4 cm separation that could be electronically subtracted to form a first-order or a second-order gradiometer. The system was very compact with overall diameter 12.5 cm, height 30 cm and mass 6 kg, and could be piggybacked onto the gantry of our 37 channel LTS system (Magnes, 4D Neuroimaging, San Diego).

The experimental protocol was approved by our institutional human subjects committee. FMCG recordings were made with the HTS system after using ultrasound to locate the fetal heart and the LTS system to find the position of maximal fMCG amplitude on the mother's abdomen. The signal was sampled at 1250 Hz. An on-line filter with passband 0.3-500 Hz and an off-line filter of passband 1-80 Hz were applied to remove noise. Averaging of consecutive complexes was used to increase the signal-to-noise ratio. During each session a recording was obtained with the LTS system for comparison with the HTS system. All recordings were made within a magnetically-shielded room (MSR).

To assess the ability of the HTS system to operate in a noisy environment, we opened the door of the MSR and measured noise spectra with the system located at various distances from the door opening.

RESULTS

Shown in Fig. 1 are power spectra of the three HTS SQUID channels measured inside a small μ -metal enclosure. The magnetic field resolutions at 1kHz are 109 fT/(Hz)^{1/2}, 155 fT/(Hz)^{1/2} and 51 fT/(Hz)^{1/2}; however, the noise increases strongly at frequencies below about 20 Hz.

The MCG from an adult subject is displayed in Fig 2, showing the outputs of the three magnetometers as well as four electronically formed gradiometers. The peak-to-peak amplitude of the QRS was several times greater for the HTS system (130 pT) than for the LTS system (50pT, not shown) recorded from the same subject in the same session. This is expected because the LTS system is configured as a first-order gradiometer rather than a magnetometer. Also, the tail gap is 1.5 cm for the LTS system vs. 0.7 cm for the HTS system.

Serial measurements were performed on two normal fetuses. In the raw tracing of Fig 3, the QRS complexes of a 36-week fetus are clearly visible above the maternal MCG interference and background noise. After averaging, the morphology of the signals from the HTS and LTS systems shows good agreement. The signal amplitudes are larger for the HTS system than for the LTS system for the same reasons noted above for the adult data. However, the HTS system noise level is so high that the overall signal-to-noise ratio is relatively poor. FMCG signals less than about 5 pT were difficult to resolve, and fetal P-waves could not be seen in the raw HTS system recordings.

The SQUIDs maintained flux-lock at all locations within the shielded room, but failed to operate outside the MSR.

DISCUSSION

The performance of HTS SQUIDs has steadily improved over the years, and the white noise performance of some HTS SQUIDs is approaching that of LTS SQUIDs; however, HTS SQUIDs with low white noise tend to show high levels of low-frequency (1/f) noise. The HTS SQUIDs used in this study have adequate sensitivity to resolve the QRS complex of the near-term fetus; however, the success rate at earlier gestational ages is low and the fetal P-wave cannot be resolved in the raw tracings. Furthermore, for widespread clinical application of fMCG the elimination of the MSR is highly advantageous, but the HTS system failed to maintain flux-lock outside the MSR. Further improvements in HTS SQUID technology can be

expected—and current HTS technology may be adequate for less demanding biomagnetism applications—but the results obtained here suggest that significant obstacles must be overcome before HTS SQUIDs can be utilized for fMCG.

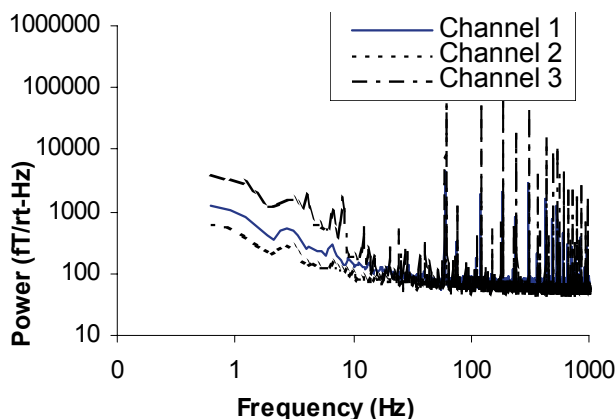


Figure 1. Power spectra taken in a μ -metal enclosure at Tristan for 3 HTS SQUID channels.

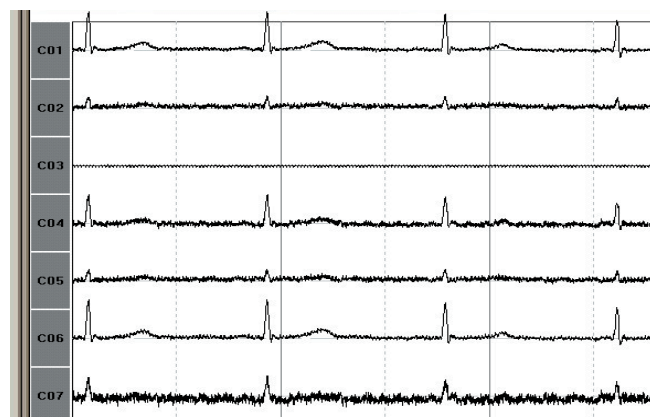


Figure 2. Time series showing adult MCG on the signal (ch1-3) and derived channels with HTS system. Vertical bar (right) = 100 pT.

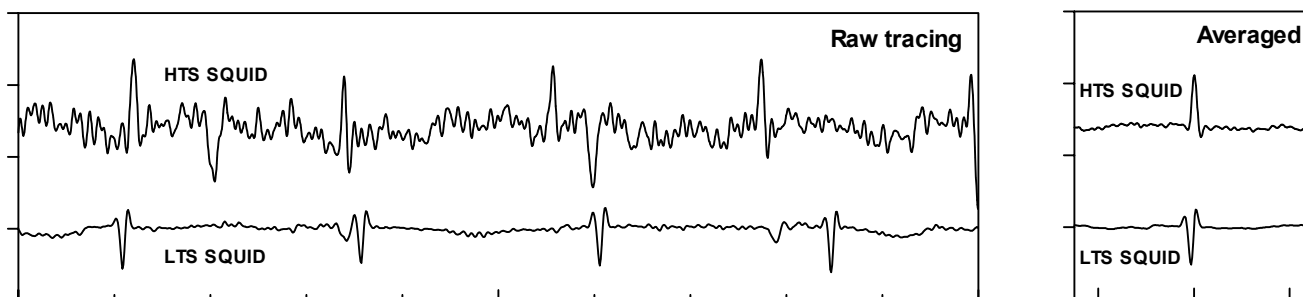


Figure 3. Raw and averaged fMCG tracings taken with HTS and LTS SQUID systems. The vertical tick marks are 5pT apart and the horizontal tick marks are 0.2-sec apart. The HTS and LTS waveforms were averaged for 38-sec and 20-sec, respectively.

ACKNOWLEDGEMENTS

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Influence of fetal age and gender on cardiac time intervals in fetal magnetocardiography

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ABSTRACT

Aim of this work was to investigate the dependency of fetal CTI on gestational age and gender in a substantial sample of subjects during normal pregnancy. A total of 230 fetal magnetocardiograms were obtained in 47 healthy fetuses between the 15th - 42nd week of gestation. In each signal averaged fetal PQRST course the following CTI were determined: P wave, PR interval, PQ interval, QRS complex, ST segment, T wave, QT and QTc interval. Using regression analysis, the dependency of the CTI were examined with respect to gestational age and gender. Linear and nonlinear regression analysis established strong dependency on age for the P wave and QRS complex as well as an identifiable trend for the PR and PQ intervals. Gender differences were found only for the QRS complex from the 31st week onward ($p < 0.05$). The results show that, from approximately the 18th week to term, fetal CTI which quantify depolarization times can be reliably determined using magnetocardiography. The clear dependency on gestational age that these CTI show seems to be linear for the P wave and nonlinear for the QRS complex. For the duration of the latter, gender plays an increasing role towards term. We conclude that these CTI may be used to quantify fetal growth.

KEY WORDS

magnetocardiography; gestational age; gender; cardiac time intervals.

INTRODUCTION

Numerous studies have been performed using magnetocardiography which demonstrate changes in the duration of fetal cardiac time interval during gestation [Quinn, 1994] [Leuthold, 1999] [Kähler, 2002]. These studies differed with respect to which CTI were examined, the number of subjects and acquisitions investigated, their range over different gestational ages and the configuration of the MCG system used in acquisition. The CTI most often studied have been the QRS complex, the P wave and the PR interval. Although there is general agreement that these intervals increase in duration as the fetus matures, the values show differences between studies [Stinstra, 2002] and systematic examinations under relatively uniform conditions in large samples are rare. Also, there is an overall lack of data with respect to other intervals, in particular those reflecting repolarization times. Furthermore, there is reason to expect that a further factor influencing CTI duration may be gender [Brambati, 1980]. This work investigated the dependency of fetal CTI, summarizing both depolarization and repolarization times, on gestational age and gender in a substantial sample of subjects during normal pregnancy. The goal was to produce a large, consistent body of data which may serve as a preliminary reference for future work.

METHODS

We examined 43 women in 47 healthy pregnancies (32 ± 3 years of age) of whom 28 (60%) carried male fetuses and 19 (40%) female. We recorded 255 FMCGs between the 12th and 42nd week of gestation, of which 230 displayed sufficient signal quality to enable evaluation. All of the 25 recordings which could not be evaluated were prior to the 20th week and no data was available before the 15th week. We obtained on average 4.9 ± 4.3 per fetus (range 1-23). In the period from the 18th to the 39th week, the number of recordings per week of gestation lay between 6 and 14 (10.0 ± 2.3), before the 18th and after the 39th week the number of recordings was between one and three per week of gestation. Of all evaluated recordings, 116 (50.4%) were performed in male fetuses, 114 (49.6%) in female. The study was approved by the local ethics committee and all mothers gave written informed consent.

FMCGs were acquired using a 61 channel biomagnetometer (Magnes 1300C, 4D Neuroimaging, San Diego) in 162 cases and 68 FMCGs were recorded using a 37 channel system (Krenikon, Siemens, Erlangen). Previous work has shown that the estimation of CTI is comparable for these two systems [Van Leeuwen, 2004]. For data acquisition the mothers were in a supine position with the biomagnetometer placed as close to the abdomen as possible. Data were usually recorded for 5 minutes at a sampling rate of 1 kHz and with a bandpass of 1-200 Hz. To reduce the effects of external noise, all measurements were performed in a standard shielded room (AK3b, Vacuumschmelze, Hanau).

In each set of data, after digital subtraction of the maternal artifact, fetal beats were identified on the basis of a good match ($r \geq 0.90$) with a representative fetal QRS signal template (generally >300 beats). In the averaged data, the onsets and ends of the P wave, QRS complex and T wave were marked according to standard criteria [Grimm, 2003]. These time points were then used to calculate the duration of the following contiguous intervals: P wave = $P_{end} - P_{onset}$, PQ interval = $Q_{Rsonset} - P_{end}$, QRS complex = $Q_{Rsend} - Q_{Rsonset}$, ST segment = $T_{onset} - Q_{Rsend}$ and T wave = $T_{end} - T_{onset}$. Furthermore, the following composite CTI were determined: PR interval = P wave + PQ interval and QT interval = QRS complex + ST segment + T wave. Also, the rate corrected QT interval (QTc) was calculated according to Bazett's formula. In some traces, signal quality did not permit the unequivocal identification of the timing of an event and the corresponding CTI were not determined.

Simple linear as well as nonlinear regression was used to estimate the parameters governing the change of the CTI over gestational age. For any interval, the model that demonstrated the best fit, based on the coefficient of determination, was chosen as most appropriate. To examine the differences between male and female CTI at a specific week of gestation, all values of each gender were projected to that week on the basis of each sex's best fitting model and the projected group values compared using Mann-Whitney U test. Statistical significance was assumed at a level of 0.05.

RESULTS

Atrioventricular conduction and ventricular depolarization times could be determined dependably whereas the T wave was often difficult to detect. Based on the coefficient of determination (r^2), linear and nonlinear regression analysis established strong dependency on age for the P wave and QRS complex as well as an identifiable trend for the PR and PQ intervals (see Table and Figure). Gender differences were found only for the QRS complex from the 31st week onward ($p < 0.05$).

Table: Best fit linear/nonlinear regression parameter of fetal cardiac time intervals with respect to gestational age.

	regression type	N	r ²	y-intercept (ms)	slope (ms/week)	p	slope (ms/week ²)	p
P wave	linear	228	0.67	14.0	1.37	<0.001		
PQ interval	non-linear	228	0.13	14.2	3.38	0.021	-0.07	0.008
PR interval	non-linear	228	0.21	20.0	5.35	<0.001	-0.08	0.002
ln(QRS)	non-linear	230	0.66	1.8	0.60 [ln(week)]	<0.001		
ST segment	linear	217	0.01	60.4	0.32	0.169		
T wave	linear	216	0.00	126.0	0.00	1.000		
QT interval	linear	216	0.07	205.8	1.24	<0.001		
QTc interval	linear	216	0.06	326.6	1.65	<0.001		

DISCUSSION

The work presented offers a stable basis for the study of the relationship between the CTI and gestational age: the number of cases is high and many factors causing a potential bias resulting from different recording and evaluation techniques factors were avoided. Thus one may expect the observed trends and variance to reflect more closely the physiological factors involved. The results suggest a nonlinear dependency for intervals containing the PQ interval and QRS complex, all others being linear whereby the influence of age on CTI reflecting repolarization are negligible or non-existent. The nonlinear nature of the increase in QRS duration during pregnancy is in accordance with estimations of fetal cardiac dimensions and mass based on ultrasound which more often than not, are described more adequately using quadratic polynomials. Of particular interest is the observation of a trend to lower values for females after the 30th week. This is consistent with gender based differences in pediatric populations and the fact that females are characterized by a lower birth weight than males. This will be of importance, for example, when investigating the possible association between growth retardation and CTI in order to avoid masking reduced QRS duration in male subjects. We conclude that these CTI may be used to quantify fetal growth and that gender plays an increasing role in the third trimester.

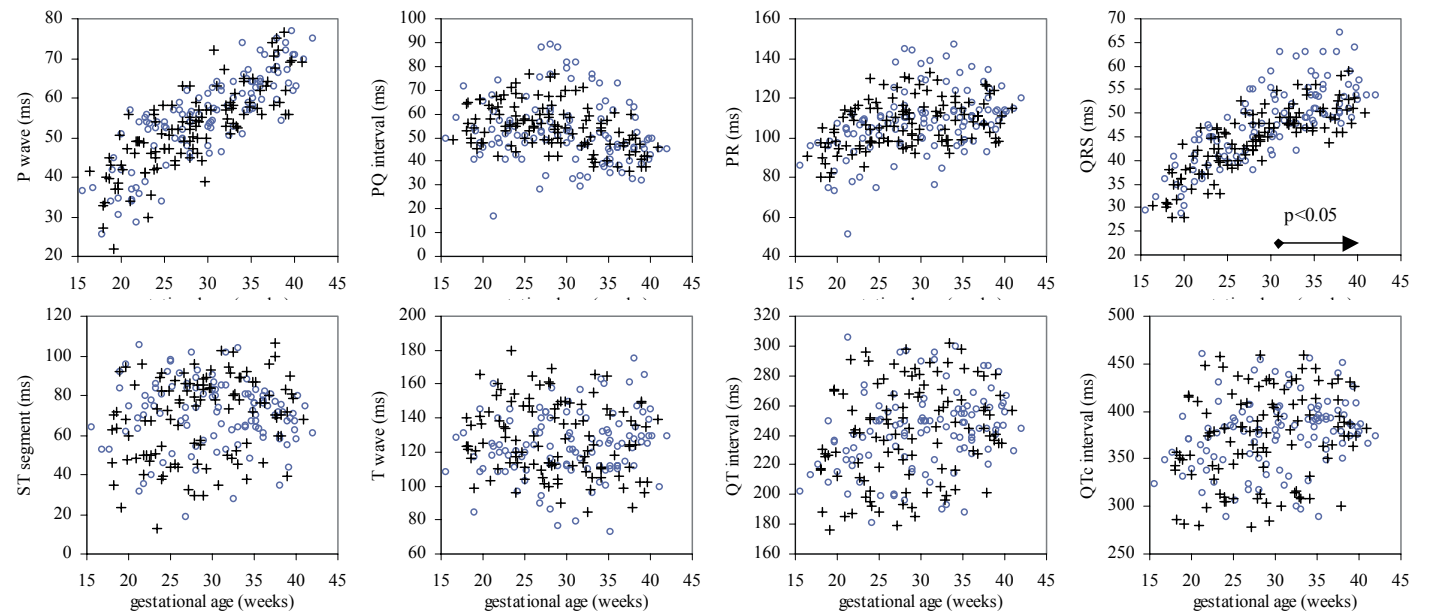


Figure: Scatter plots of fetal CTI vs. gestational age (males o, females +). Significant male/female difference for ORS after the 30th week

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Assessment of fetal growth on the basis of signal strength in fetal magnetocardiography

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ABSTRACT

Fetal magnetocardiography has been used to assess the growth and development of the fetus on the basis of the duration of fetal cardiac time intervals. A general consensus exists that P wave and QRS complex increase with gestational age, reflecting the change in cardiac muscle mass. The latter should, in principle, lead to an increase in signal strength over gestation. In this work we examined two approaches for determining QRS signal strength in a healthy fetus on a weekly basis in the second and third trimester. Twenty-two fetal magnetocardiograms of the same fetus were obtained using a 61 channel Magnes 1300 biomagnetometer (20th - 42nd week of gestation). In the signal averaged fetal beat produced at each week, signal strength was assessed on the basis of 1) the peak-to-peak QRS signal amplitudes and 2) the strength of an equivalent current dipole (ECD) computed at R peak. The quality of the variables was assessed on the basis of the correlation to week of gestation and by comparison to changes in QRS interval duration. All values increased with advancing gestation and regression analysis suggested a nonlinear dependency on age. ECD strength reflected gestational age slightly more reliably ($r^2=0.93$) than signal amplitude values (mean, median, maximum: $r^2=0.89, 0.88, 0.85$, respectively). ECD strength and mean signal amplitude also correlated well ($r=0.97, p<0.0005$.) Values calculated from QRS complexes determined immediately before and after a clear change in fetal position (acquisition in week 24) demonstrated a certain instability in both approaches. Nonetheless, the overall correlation of the amplitude to gestational age compared favorably with that of QRS complex duration. This indicates that not only magnetocardiographically determined fetal cardiac time intervals but also signal strength may be used to assess fetal growth.

KEY WORDS

fetal magnetocardiography; gestational age; signal amplitude; equivalent current dipole; QRS complex.

INTRODUCTION

The assessment of the growth and development of the fetus using magnetocardiography (MCG) is usually based on the duration of fetal cardiac time intervals. Numerous studies have shown that, in particular the P wave and QRS complex increase in length as pregnancy progresses, e.g. [Quinn, 1994] [Stinstra, 2002(a)]. These changes are presumed to reflect the increase in cardiac muscle mass associated with fetal growth [Van Leeuwen, 2004]. This enlargement should be associated with increased MCG signal strength and a number of studies have described corresponding findings using signal amplitude [Li, 2002] and dipole strength [Kandori, 1999]. However, determination of signal strength is not quite unequivocal as a number of confounding factors affecting measured signal strength exist. These include the orientation and distance of the fetal heart relative to the sensing system and the geometry of the volume conductors [Stinstra, 2002(b)]. Furthermore, examining signal strength interindividually of fetuses at varying gestational ages will increase the overall range of values and make it more difficult to estimate the variance within the single fetus. In order to examine intraindividual changes, we performed close meshed fetal MCG acquisition over the second and third trimester in a single pregnancy and estimated QRS signal strength and compared changes over gestation to those in QRS duration.

METHODS

Twenty-two fetal magnetocardiograms of the same fetus in a healthy pregnancy were obtained on a weekly basis between the 20th and 42nd week of gestation. All data acquisitions were performed using a 61 channel Magnes 1300 biomagnetometer (Magnes 1300C, 4D Neuroimaging, San Diego). With the mother in a supine position, the slightly curved, circular sensor (diameter 104 cm, radius of curvature 52cm) enabled the complete coverage of her abdomen from the pubis to the xyphoid. With the sensor just above the abdomen, data were recorded for at least 5 min. at a sampling rate of 1 kHz and with a bandpass of 1-200 Hz. Extraneous noise was minimized by performing data acquisition in a standard shielded room (AK3b, Vacuumschmelze, Hanau).

In each set of data, after digital subtraction of the maternal artifact, fetal beats were identified on the basis of a good match ($r \geq 0.90$) with a representative fetal QRS signal template (generally »300 beats). In the averaged data, the onsets and ends of the QRS complex were marked according to standard criteria and its duration calculated as $QRS_{end} - QRS_{onset}$. Signal strength was estimated in two ways. Peak-to-peak QRS signal amplitude was determined in each channel and characterized for the data set by the mean, median and maximum value, expressed in pico Tesla (pT). Secondly, at R peak a best fitting equivalent current dipole (ECD) was localized in a homogeneous sphere (radius 50cm) and its magnitude in nano-ampere-meters (nAm) was determined. In one data set (in week 24), there was a single marked change in fetal position part way through the acquisition with a concomitant change in QRS amplitudes and morphology. This data set was divided into two traces, one before and one after the change, and both were examined separately.

The relationship of these parameters to gestational age was examined using linear and nonlinear regression analysis and the coefficient of determination (r^2) was used to quantify the goodness of fit. The relationship between signal strength parameters and QRS duration was also investigated.

RESULTS

All values increased with advancing gestation (Fig. 1a, 1b, 1c) and regression analysis suggested a nonlinear dependency on gestational age which could, more often than not be appropriately characterized by $\ln(y) = a + b \cdot \ln(\text{age})$. The r^2 was high for signal amplitude values with the central variables for location, the mean ($r^2=0.89$) and the median ($r^2=0.88$), performing better than the maximum ($r^2=0.85$). ECD strength reflected gestational age slightly more reliably ($r^2=0.93$) than signal amplitude values. Although in itself dependably reflecting gestational age, QRS duration ($r^2=0.81$) performed poorly in comparison. The changes in duration and signal strength also associated well (QRS vs. mean, median and maximum amplitude as well as ECD strength: Spearman $r = 0.92, 0.93, 0.88$ and 0.86 respectively, Fig 1d). Signal strength values calculated from QRS complexes determined in different fetal positions (acquisition in week 24, Fig. 1a, 1b) displayed substantial relative differences in peak-to-peak amplitude (mean: 0.3 vs. 0.8 pT, median: 0.3 vs. 0.6 pT, maximum: 0.7 vs. 2.6 pT) and ECD strength (127 vs. 231 nAm).

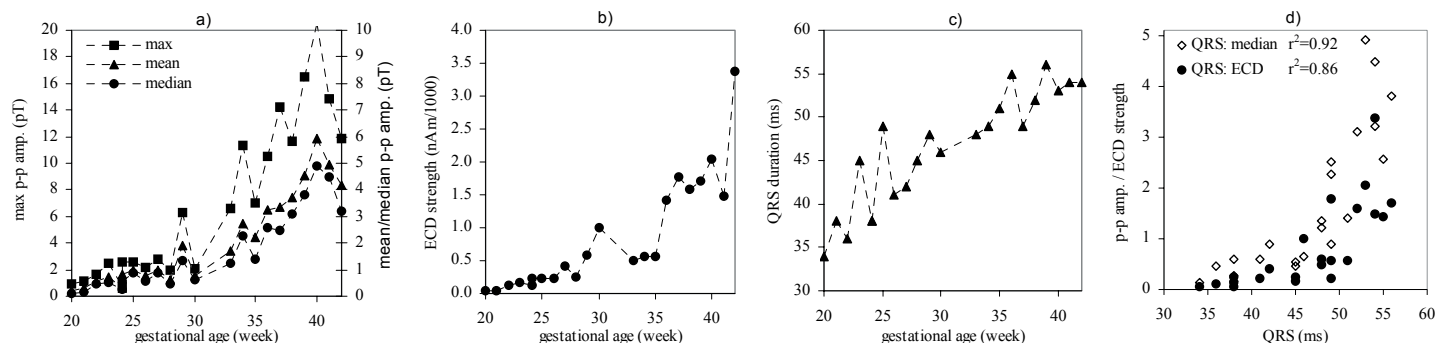


Figure 1: changes over gestational age in a) QRS maximum, mean and median peak-to-peak signal amplitude, b) ECD strength at R peak and c) QRS interval duration; d) scatter plot comparing QRS duration and median QRS amplitude as well as ECD strength

DISCUSSION

The results suggest that not only magnetocardiographically determined fetal cardiac time intervals but also signal strength may be used to assess fetal growth reliably. Indeed, in the one case we studied here, the parameters used to quantify strength demonstrated a better association with gestational age than QRS duration. This was surprising, as confounding factors not related to developmental status - in particular fetal location - have the potential to strongly influence the measured quantities. This was demonstrated clearly in the values obtained from one acquisition, determined immediately before and after an apparent change in fetal position. They showed the instability of both the signal amplitude and the ECD approaches, although the latter not affected as strongly. In contrast, the change in QRS morphology in individual channels resulting from the re-positioning did not lead to a change in measured QRS duration.

In spite of the sensitivity to extraneous factors, the relationship of signal strength to week of gestation was fairly stable in this individual. Overall ECD reflected signal strength changes with respect to fetal age best and maximum peak-to-peak amplitude showed the weakest association. ECD calculation makes specific assumptions in the interpretation of the data and, as long as the magnetic field has a sufficiently dipolar character, ECD strength may come closer to reflecting true signal magnitude than the amplitudes measured at the abdominal surface. The biomagnetometer system used in this study had excellent coverage of the frontal maternal abdomen and assured clear dipolar fields in most acquisitions. Furthermore, the curvature of the measurement plane permitted the partial registration of field components in the maternal caudal-cranial / left-right plane. On the other hand, an accurate estimation of absolute fetal cardiac signal strength on the basis of magnetometer cannot be expected [Stinstra, 2002(b)]. Nonetheless there is a value in the relative change of the estimated signal strength and the results suggest that it can be used to estimate fetal growth and development. Further work must be done to examine the parameters intra- and interindividually in larger groups of subjects in order to determine the potential for clinical applications.

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Phase coordination in magnetocardiographically recorded fetal and maternal heart rates

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ABSTRACT

In the period before birth mother and fetus are closely physiologically intertwined and evidence exists that indicates an influence of the maternal condition on fetal heart rate. Goal of this work was to develop methods for the investigation of coordination between fetal and maternal cardiac systems on the basis of simultaneously recorded fetal and maternal magnetocardiograms (MCG). Using a 61 channel biomagnetometer, 195 MCG were recorded in 69 pregnancies (16th-42nd week of gestation) at a sampling rate of 1 kHz. In each recording, fetal and maternal R-peaks were determined to an accuracy of 1 ms. The timing of n fetal R-peaks in relation to m maternal RR intervals for different $n:m$ ratios was analyzed in synchrograms based on the stroboscopic technique. Epochs of heart rate coordination ≥ 10 s were determined using a threshold-based method identifying $n:m$ ratios. The number of coordination epochs (CE) found overall, per $n:m$ ratio and per recording as well as gestational age, the duration of CE and $rmssd$ of fetus and mother during the CE were determined. These were compared to those found in surrogate pairs of fetal and maternal data sets. In the epochs of the original data, we found a phase preference for specific $n:m$ coupling ratios which was not apparent in the surrogate data. The results demonstrated that methods exist that permit the examination of fetal-maternal heart rate coordination. Application of these methods suggests that under appropriate conditions the maternal heart beat may exert a weak forcing effect on the fetal cardiac cycle.

KEY WORDS

magnetocardiography; fetal maternal interaction; gestational age; synchronization; synchrogram; heart rate variability.

INTRODUCTION

In the human life cycle, there is no time when two individuals are more closely physiologically intertwined than in the period before birth. The prenatal condition thus represents a unique opportunity to investigate physiological interaction between two individual organisms. With respect to cardiac interaction, evidence exists that indicates an influence of the maternal condition on fetal heart rate [Hildebrandt, 1979]. The published evidence which suggests fetal-maternal cardiac interaction is based on only few cases. We examined concurrent fetal and maternal RR interval time series extracted from magnetocardiographic recordings in a relatively large sample covering the 2nd and 3rd trimester of pregnancy. The goal of this work was to develop methods to aid in the identification and classification of such coordination. In particular the examination of simultaneously recorded fetal and maternal heart rates may reveal to what extent coordination exists between these two cardiac rhythms.

METHODS

We studied 69 pregnant women (age: 30.6 ± 4.5 years; 33 nullipara, 28 primipara and 7 multipara, 1 not reported) between 16th - 42nd week of gestation. Fetuses with persistent arrhythmias were excluded. Altogether 195 magnetocardiograms (MCG) were obtained, 53 in the 2nd and 142 in the 3rd trimester. MCG were recorded using a 61 channel biomagnetometer (MagneS 1300C, 4D-Neuroimaging, San Diego) in a shielded room (Vakuumschmelze, Hanau, Germany). This system enables the simultaneous acquisition of both the fetal and the maternal magnetocardiogram (MCG). The sensors are arranged concentrically on a slightly curved surface ($r_c = 52$ cm) with 800 cm² area of coverage. MCG were recorded for 5 minutes at a sampling rate of 1kHz and a band pass of 1-200 Hz.

In each recording, fetal and maternal R-peaks were determined to an accuracy of 1 ms. The relative timing of the fetal R peak with respect to the simultaneous maternal RR cycle is referred to in the following as the phase φ_{mat} . Synchrograms of coordinated epochs (CE) were constructed using the stroboscopic technique [Schäfer, 1998]: the phases of the fetal R peaks φ_{mat} were plotted with respect to m maternal cycles ($m \geq 1$). This representation displays the phase of fetal R peaks within one or more maternal RR interval on a time axis. Horizontal groupings of data points indicates phase coordination. The number of parallel lines (n) in an epoch of such horizontal groupings embedded in m maternal RR intervals indicates the coupling ratio $n:m$.

CE were quantitatively determined according to the following procedure. For fixed combinations of n and m , the phase φ_{mat} was determined for each fetal R peak (index i), the absolute difference $\delta_i = |\varphi_{mat,i} - \varphi_{mat,i+n}|$ was calculated and a sliding window of length l was moved over all δ_i [Bettermann, 2002]. If, within the window, all $\delta_i < \text{threshold value } \alpha$, an CE was considered detected. Following parameters were set: The number of maternal cycles was restricted to a maximum of 4. The choice of considered combinations of n and m was based on physiologically plausible heart rate values of fetus and mother (1:1 to 9:4). Redundancies were avoided (e.g. 4:2 $\equiv$ 2:1). This led to 10 $n:m$ combinations (see Table 1). To avoid identifying short spurious epochs the window length l was set to 10 s. The threshold value α was set for each m ($m=1$: 0.06, $m=2$: 0.05, $m=3$: 0.04, $m=4$: 0.03).

In order to investigate whether the CE found were produced by numerical combinations of transient fetal and maternal heart rates instead of physiological synchronization, surrogate pairs of data sets were constructed. To do this, we adopted a procedure introduced by Toledo et al [Toledo, 2002]. We randomly recombined maternal and fetal data sets of the same week of gestation, avoiding combinations involving a mother and her own child. The resulting pairs of RR interval data sets were analyzed as described above for the real data.

The number of CE found over all, per $n:m$ ratio and per recording as well as gestational age, the duration of CE and $rmssd$ of fetus and mother during the CE were determined separately for real and surrogate data and partly compared using the Mann-Whitney U test (two-sided).

In order to examine whether there was a preference in the timing of the fetal R peaks relative to the maternal RR cycle, the phases φ_{mat} of each CE found in each data set were determined in all data sets for both the real and surrogate data. The distributions of these phases over all subjects were examined for the $n:m$ combinations of which more than 100 CE could be found (3:2, 4:3, 5:3, 7:4, see Results). For each $n:m$ combination, the number of histogram bins was set to $10 \cdot m$, corresponding to a resolution of 10 classes per maternal beat. The distributions were visually inspected for a systematic bias for specific phases.

RESULTS

930 coordination epochs (CE) were identified in the real data, 787 in the surrogate data (see Table 1). Although the absolute difference between the mean gestational age and mean fetal *rmssd* of real and surrogate data were small, they were statistically significant (see Table 2). On average the real data contained approximately 1 CE per recording more than the surrogate data. This difference was also statistically significant. No statistically significant difference was found for CE duration or maternal *rmssd*.

Table 1: Frequency of CE in real and surrogate data for different *n:m* ratios

		<i>n</i> (fetal)								
<i>m</i> (maternal)		1	2	3	4	5	6	7	8	9
		12/20	145/114							
1										
2				222/177		8/5				
3					21/13	254/230		8/8		
4						28/5		192/196		40/19

implausible
redundant
#CE real / #CE surrogate

Looking for a preference in the timing of the fetal R peaks relative to the maternal RR cycle led to varying results. Inspection of the distributions of the phases φ_{mat} of the *n:m* combinations 5:3 and 7:4 showed a bias for the occurrence of CE in specific phases in the real data but not in the surrogate (Fig. 1). This was not obvious for the combinations 3:2 and 4:3.

Table 2: Description of several variables of real and surrogate data with associated *p*-values (means $\pm$ SD).

	# CE	# CE per record	duration (ms) of CE	week of gestation	fetal <i>rmssd</i> (ms)	maternal <i>rmssd</i> (ms)
real data	930	4.8 $\pm$ 3.2	16.0 $\pm$ 8.2	29.7 $\pm$ 6.0	3.9 $\pm$ 4.3	15.0 $\pm$ 9.7
surrogate data	787	4.0 $\pm$ 2.9	15.8 $\pm$ 7.8	30.3 $\pm$ 5.9	4.1 $\pm$ 3.2	15.7 $\pm$ 10.5
<i>p</i> -value		0.028	0.572	0.036	0.002	0.152

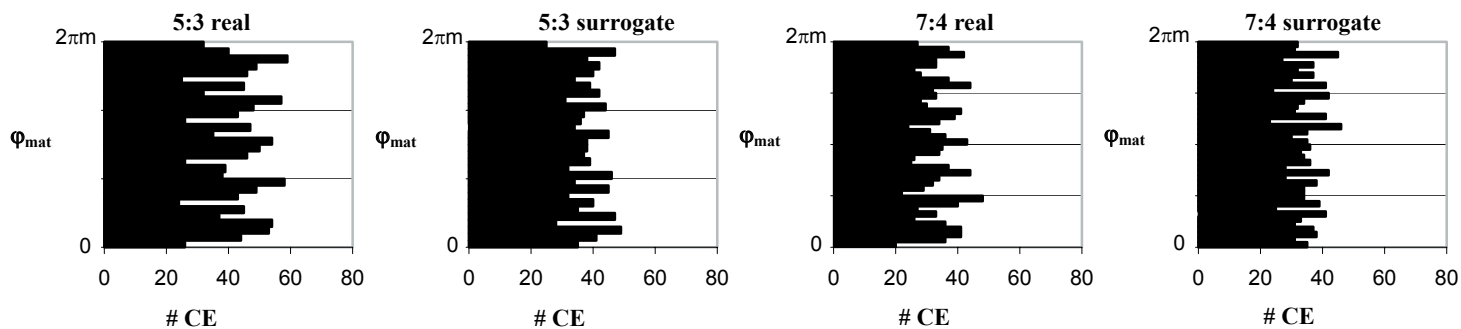


Figure 1: Phase distribution of real and surrogate data for the combinations of 5:3 (left) and 7:4 (right).

DISCUSSION

Both in terms of the single recording as well as overall, roughly 20% more CE were found in the real than in the surrogate data. This implies that most of the CE identified were due to spurious, whole number combinations of fetal and maternal heart rates. Conversely we may presume that real physiological interaction does indeed take place. It follows that criteria must be developed which will enable the discrimination between real synchronization and spurious epochs. The marginal but significant differences in *rmssd* and gestational age between real and surrogate data suggest that synchronization coincided with lower heart rate variability and earlier pregnancy. This may indicate the more likely occurrence of synchronization in a phase of fetal life with greater dependency on the mother. With progressing gestation and maturation of the fetal autonomic nervous system - reflected by increasing heart rate variability - the fetus' dependency on the mother becomes weaker. This may lead to conditions detrimental to synchronization. A further indication of synchronization may be the relative timing of fetal and maternal beats. According to the detected phase relationship, it can be presumed that the fetal rhythm is triggered by the guiding maternal pulse wave rhythm [Hildebrandt, 1979]. It is possible that a phase preference also occurred in other *n:m* combinations than 5:3 and 7:4, but was not detectable due to low numbers of CE. To improve the separation of real synchronization and numerical coordination, data collection in future studies could be performed under defined conditions (e.g. forced maternal breathing, fetal behavioural state). Furthermore, recently developed methods [Rosenblum, 2002] may aid in the examination of the direction of synchronization.

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Gradiometer for Fetal Heart Monitoring in Hospital Setting

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A single channel SQUID gradiometer specially designed for fetal heart monitoring in hospital setting was developed. The magnetometer is equipped with a wire wound third order flux transformer coupled to the SQUID sensor. The configuration of the flux transformer is optimized for the measurement of magnetic field of the fetal heart, in noisy environment, with an appropriate signal to noise ratio. The magnetocardiograph system incorporates a mechanical balancing device which enables the balancing by several orders of magnitude. This balancing method, by means of superconducting vanes, is reliable, particularly for our movable magnetometer. The system was tested in an unshielded environment as well as at bedside location in hospital. Spatial characteristic of the third order gradiometer for unshielded measurements are given. Further improvement of the signal to noise ratio of measured fetal magnetocardiogram recordings is achieved by elaborated software. Fetal MCG signals have sufficient amplitude for subsequent processing and analyses. The efficacy of the developed system shows applicability to the investigation of fetal heart activity without the requirement of shielded rooms.

Analysis of Fetal Heart Rate Variability Using Fetal Magnetocardiograms Recorded in a Magnetically Disturbed Environment

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Fetal heart rate variability (FHRV) is a useful technique for assessing non-invasively the status of autonomic nervous system of the developing fetus. The purpose of this study was to acquire fetal magnetocardiograms (fMCG) in a magnetically shielded as well as high-frequency noise environment, implement an automated QRS detection algorithm, extract RR series for fetal heart rate variability analysis and evaluate the spectral energies of the Lomb periodograms for bias due to the noisy environment. Fetal magnetocardiograms (n=17) were recorded over a period of 5 min at 9 spatial locations above the pregnant abdomen at 26 to 35 weeks gestational age (GA) by a second-order SQUID gradiometer. High-frequency noise, baseline drifts, artifacts, and occasionally maternal-MCG were removed using standard techniques of biomagnetic signal processing. Due to lower signal-to-noise ratio for GA <30, typical QRS detection sensitivity using a modified Pan-Tompkins algorithm was in the range of 70–85%. It was found that for GA ≥30 automated QRS detection sensitivity was above 98% for both shielded and noisy environments. The total spectra power, or the variance, as well as band powers at low (0.05 to 0.25 Hz) and high (0.25 to 1.00 Hz) frequencies independently, indicated an increasing trend with increasing GA. There was no evidence of bias due to lack of shielding. In conclusion, these results provide important experimental evidence supporting further studies in magnetically unshielded environments and may have an important implication for future clinical use of fetal magnetocardiography in the assessment of FHRV.

Separation of Normal and Ectopic fMCG Rhythms Using Independent Component Analysis

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OBJECTIVE: To use Independent Component Analysis (ICA) to noninvasively detect the presence of normal and ectopic fetal cardiac rhythms in fetal magnetocardiographic (fMCG) recordings. **METHODS:** Magnetocardiograms were performed on 25 fetuses at the University of Arkansas for Medical Sciences SARA (Squid Array for Reproductive Assessment) Cardiac Center. Gestational ages ranged from 21 to 39 weeks. Fifteen of the fMCG recordings exhibited known ectopic rhythms. Each recording lasted an average of eight minutes, after which an algorithm using orthogonal projection removed the interfering maternal cardiac signal. After removal of maternal cardiac signal, ICA was performed to separate the remaining signals into the independent components whose combination creates the observed signals. The results of various ICA techniques were analyzed to determine if known ectopic rhythms were identified. **RESULTS:** RUNICA, FastICA, and JADE ICA algorithms were able to find separate components for normal and ectopic rhythms in all subjects exhibiting each. Identification of the normal cardiac signals was also successfully performed in the remaining subjects. After identification of the cardiac rhythms in all subjects exhibiting normal and ectopic rhythms, the components were visually inspected to determine accuracy of the separation algorithms. The ectopic rhythms were identified with 85% (191/225) accuracy using both RUNICA and JADE algorithms. Using FastICA 97% (218/225) of the ectopic rhythms were correctly separated into the components containing the ectopic rhythms. **CONCLUSIONS:** ICA, specifically FastICA, has proved to be a valuable tool in evaluating normal and ectopic fetal heart rhythms during the antepartum period. The ability of fMCG to non-invasively record the magnetic fields emitted by the fetus with superior signal to noise ratio, the unique design of the SARA instrument, and signal processing tools like ICA allow normal and ectopic fetal heart rhythms to be independently analyzed, thereby improving fetal surveillance.

Characterization of fetal arrhythmias by means of fetal magnetocardiography in three cases of maternal obesity, fetal prone position, and oligohydramnios

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Clinical detection of fetal arrhythmias is generally performed by means of M-mode and pulsed Doppler echocardiography (fECHO), although this method is far from being ideal because it detects the mechanical activity, not the electrophysiological events. Several studies have shown the ability of fetal magnetocardiography (fMCG) to detect fetal arrhythmias directly. **Method:** we report fMCG of three patients (pts), respectively studied at the 37th, 32nd and 36th, 30th gestational week. In all patients fECHO had shown evidence of irregular fetal heart rhythm, but a satisfying cardiac visualization was impossible because of maternal obesity, or fetus in a constant prone position, or intra-uterine growth retardation and oligohydramnios. In the third patient fECHO had evidenced minor pericardial effusion and digoxin therapy was given. fMCG was recorded for 5 minutes with the flat 77-channel magnetometer (sensitivity 5 fT/Hz^{1/2}) working in shielded room at ITAB (Chieti University). Independent Component Analysis (FastICA algorithm) was used to extract the fetal signal from fMCG raw data. Smoothing of the extracted fetal traces was performed, if necessary, to improve the S/N ratio. **Results:** The quality of all reconstructed fetal traces allowed real-time beat-to-beat detection of supraventricular extrasystoles (SVE), with/without aberrant ventricular conduction and/or atrio-ventricular block. Selective averaging of sinus and SVE helped the accurate estimate of QRS duration. Heart rate variability parameters were also computed in time and frequency domains. **Conclusions:** Reliable reconstruction of fetal cardiac signals allowed the non-invasive beat-to-beat detection of, even transient, fetal arrhythmias and the monitoring of antiarrhythmic therapy effects during pregnancy.

Time course of heart rate and cardiac time intervals variability: a mother-fetus match study

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Objective: A clinical technique for the assessment of morphological and temporal parameters of cardiac electrical activity in the fetus in relation to gestation advance is, at present, mostly required. Fetal magnetocardiography (fMCG) provides reliable recordings of fetal electro-cardiological activity throughout the second half of pregnancy. Aiming at investigating the correlation between fetal and maternal well-being during gestation, we propose a method for the detection and quantification of fetal rhythm in relation to maternal state. It consists in a coupled assessment of fetal and maternal heart rate variability (HRV) parameters in time and frequency domains, and in a coupled quantitative description of fetal and maternal cardiac time intervals variability. **Method:** 55 fMCG and simultaneous maternal ECG from singleton pregnancies between the 22nd and 37th gestational week were analyzed. Independent Component Analysis (ICA) was used to reconstruct the time course of fetal electro-cardiological activity from raw fMCG. A software package was developed to perform HRV analysis (reconstruction of RR interval sequences, tachogram, RR interval distribution, power spectral density, time and frequency parameters such as heart rate, SDNN, RMSSD, NN50, pNN50 and HRV index) and variability study of cardiac time intervals (P-QRS-T intervals quantification on a beat-to-beat basis). **Results:** The good quality of the fetal signals reconstructed with ICA and the high detection rate of cardiac waves on real-time traces (94%) allows performing a reliable mother-fetus match-study of time and frequency parameters related to cardiac activity useful to quantify any maternal influence on fetal well-being. **Conclusions:** fMCG and the reliable ICA reconstruction of the time course of fetal cardiac activity allow an adequate time and frequency analysis of simultaneous fetal and maternal cardiac signals that may provide an important tool to current methods of antenatal monitoring.

Influence of fetal growth restriction on linear and non – linear parameters of fetal heart rate variability (HRV) investigated by fetal magnetocardiography (FMCG)

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Objectives: We compared linear and non linear parameters of heart rate variability (HRV) in 50 normotrophic and 25 growth restricted fetuses (7 of them with brain sparing) between 26 – 40 weeks of gestation using a 31 – channel – SQUID biomagnetometer in a shielded environment. **Methods:** The data were analysed with MATLAB calculating following parameters of *time domain*: mean heart rate (mean HR), standard deviation of NN-intervals (SDNN), Square root of the mean of the sum of the squares of differences between adjacent NN-intervals (RMSSD), standard deviation of differences between adjacent NN intervals (SDSD), number of NN interval differences above 5, 10 and 20 ms (PNN5, PNN10, PNN20), triangular index (HRVtri) and triangular interpolation of NN interval – histogram (TINN), *frequency domain*: Power in low frequency range (0,04-0,15 Hz), (LF), in high frequency range (0,15-0,4 Hz), (HF), Total power (TP), Ratio LF to HF (LF/HF), and *complexity*: Auto Mutual Information (AMIF) and Auto Correlation Function (ACF). **Results:** 1. Heart rate variability and complexity increase with growing gestation. 2. In growth restricted fetuses the linear parameters were reduced and the frequency domain and complexity parameters were increasing faster than in normotrophic fetuses. 3. The complexity parameters were reduced in the subgroup of growth restricted fetuses with brain sparing effect compared to those without brain sparing and to the normotrophic fetuses. **Conclusions:** The increasing values of the parameters of heart rate variability and complexity indicate a maturation of the autonomic nervous system of normotrophic as well as growth restricted fetuses mainly under the influence of the parasympathic system. Complexity parameters seem to be sensitive indicators for an alteration of the cardiac regulation in case of brain sparing.

Complete fetal mapping reconstruction by means of Independent Component Analysis for cardiac source modeling

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Objective: Independent Component Analysis (ICA) is a mathematical approach suitable for reliable fetal signals reconstruction from fMCG recordings. ICA showed to have higher performance, in terms of cardiac waves timing and morphology, than methods based on the averaging and subtraction of the maternal beat from the recorded traces. As regards the use of ICA in the processing of fMCG data sets, the major drawback of this technique is the constraint of having only one retrieved fetal signal from a large number of input traces, hence prohibiting its use in case of magnetic source localizations that need reconstructing the time course of magnetic maps throughout the cardiac cycle. Aiming at overcoming this problem, we propose an ICA-based method for the reconstruction of as many fetal traces as recorded fMCG signals with a high detection rate (more than 90%).

Method: fMCG signals were recorded with a multi-channel system working in shielded room, with 1 kHz sampling frequency and 0.016 – 250 Hz recording bandwidth. Among the available ICA algorithms we chose FastICA for its computational features. For each fMCG data set, the 55 recordings were grouped in 9 clusters from which 9 fetal signals were retrieved; by interpolating them with appropriate weights, we reconstructed fetal traces for all 55 channels; the correct amplitudes and polarities of all traces were restored using information from the original recordings.

Results: This method allowed reconstructing a complete set of 55 accurate fetal signals that can be used for cardiac mapping and localization purposes. Using an ECD model, the position, direction and intensity of the source of cardiac activation can therefore be determined. **Conclusions:** The combination of FastICA with adequate interpolation techniques was successful in reconstructing an entire set of fetal traces with the exact spatial and temporal characteristics, useful for a variety of clinical applications.

Prenatal diagnosis of a long QT syndrome by fetal MCG in an unshielded environment

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Objectives: To diagnose a fetal long QT syndrome (LQTS) using fetal magnetocardiography (fMCG) by a hereditary KCNQ1 gen mutation.

Methods: Fetal MCG was recorded in a case of fetal bradycardia suspected long QT syndrome during 30 weeks of gestation. The mother suffered from a LQTS caused by a heterozygote mutation in codon 251 leucine-to-proline of KCNQ1 gen and was treated with metoprolol. Measurements were performed with the help of a newly developed SQUID system with three first-order integrated planar SQUID gradiometers and three orthogonal magnetometers as magnetic field reference in unshielded environment. The sensors are fabricated on the basis of the Nb/AlO_x/Nb technology. Their intrinsic noise corresponding to a field resolution in one loop is better than 3 fT/sqrt(Hz) and the balance is better than >10⁻⁴. Two of the gradiometers were used for measurements of fetal heart signal and the third one as a reference to build second-order gradiometers electronically. The SQUID signals were digitized using 16-bit ADC and digitally filtered. **Results:** A fetal bradycardia of 110 bpm and loss of variability was detected by cardiotocography. The fetal MCG revealed a prolonged fetal corrected QT-interval of 0.537 s. The postnatal electrocardiogram recorded after a term delivery coincided with prenatal MCG showing a QT-interval of 0.54 – 0.56 s. A genetic analysis confirmed the same heterozygotic gene mutation in the newborn as in their mother. **Conclusion:** Unshielded measurements of the fetal MCG are reliable for the prenatal diagnosis of long QT syndrome.

Expanding Clinical Application of Fetal Magnetocardiography

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The clinical utilization of fetal Magnetocardiography (fMCG) in the management of fetal arrhythmia cases is rapidly expanding. In this center where fMCG is available within a 3 hour commute for the pregnant patient, utilization of such services are high. When the patient perceives through counseling that the data obtained may enhance clinical management of the fetal disease process, patient refusal has been low. In the evaluation of fetal arrhythmias by fMCG, the following clinical situations have been observed in decreasing frequency: 1) The pre-referral diagnosis was correct, and fMCG provided additional mechanism-specific information which did not alter the strategic clinical care plan, 2) The pre-referral diagnosis was correct, and fMCG provided additional mechanism-specific information that significantly altered the clinical care plan, 3) The pre-referral diagnosis was substantially incorrect, and fMCG led to changes in clinical care which likely would not have impacted survival, and 4) The pre-referral diagnosis was mostly incorrect, and fMCG led to changes in clinical treatment which likely improved fetal outcome. Changes in clinical care included the following in order of decreasing frequency: 1) initiation of specific laboratory tests (drug level, SSA/SSB antibody, etc), 2) altering drug dosing regimens, 3) altering drug choice, and 4) delivery of the fetus. In only one case was fMCG the only modality available to correctly diagnose the fetus, and this fetus had Long QT Syndrome. Other diagnoses for which fMCG was an important clinical diagnostic modality included supraventricular tachycardia, ventricular tachycardia, atrioventricular block, and persistent ectopy. Frequency of referrals for each diagnosis depended on the lethality of the diagnosis, with over 80% of SVT and AV block patients managed during the past 2 years undergoing the procedure. Primary indications for not sending a patient for fMCG have included gestation > 37 weeks, premature labor, treatment initiation for the fetal arrhythmia, and patient refusal. No complications from the procedure or associated travel have been encountered. Conclusion: fMCG is frequently utilized in the clinical management of fetal arrhythmia patients when it is available within a 3 hour commute.

Assessment of Normal and Fetal Arrhythmia QT Intervals by Fetal Magnetocardiography

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In order to study fetal cardiac QT interval, fMCG were obtained for 100 subjects, of whom 76 were normal pregnancy from 17 to 39 weeks gestation, 14 had supraventricular tachycardia (SVT) from 18.5 to 34 weeks gestation, 9 had complete heart block (CCHB) from 23 to 37 weeks gestation, and one had long QT syndrome with Torsade de pointes at 31 weeks gestation. QT and RR interval, and the signal amplitude of the T-wave and QRS were measured after signal averaging of the data. Corrected QT (QTc) was determined using the Bazett's formula. Values of QT, QTc, the signal amplitude of the T-wave and the T/QRS ratio as a function of gestational age were obtained. The earliest detection age of QT for normal subjects was 17 weeks, and the detection rate of QT was about 47%. The QT interval for normal subjects was 207 to 323 msec, and the QTc value was 0.33 to 0.48. The access rate of the T-wave for SVT subjects was 100%, but the measuring rate of QT was about 50%. The failed measurement of QT was caused by being unable to determine the end of T-wave due to overlap of P- and T-wave. The QT interval for SVT subjects was 166 to 227 msec, and the QTc value was 0.32 to 0.43. The detection rate of QT for CCHB subjects was 100%, the QT interval was 459 to 624 msec, and the QTc value was 0.49 to 0.6. The gestational age dependency of QT, QTc, signal amplitude of the T-wave and T/QRS ratio were also analyzed. FMCG can successfully assess QT interval for both normal and fetal heart arrhythmia subjects. QT abnormalities may have important prognostic implication in clinical management of fetal heart arrhythmia subjects.

Auditory evoked magnetic fields to speech stimuli in newborns – effect of sleep stages

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ABSTRACT

The aim of the study was to examine whether a newborn can detect changes inside a speech stimulus consisting of a fricative followed by a vowel /su/. In addition, we studied possible effect of the two sleep stages (active and quiet sleep) on the evoked magnetic responses. In young children (6 years), the same stimulus evokes a prominent deflection, consisting of two peaks. The first one (P1m) is evoked by the beginning of the fricative consonant and has a latency of about 150 ms. The second peak (P2m) with a latency of 340 ms, is evoked by the switch to the vowel [Pihko et al, submitted]. In newborns ($n = 10$), the waveform resembled that of the older children but latencies of the corresponding peaks were longer, 190 and 435 ms, correspondingly. The results suggest that already the newborn brain detects the change inside the auditory speech stimulus, namely the fricative sound changing into a vowel. However, the immaturity of the brain is reflected in the prolonged latencies. In addition, the responses were higher in amplitude in quiet sleep than in active sleep. ($F(1,9) = 36.5$; $p < 0.0002$). This is in line with the enhanced somatosensory magnetic fields to tactile stimulation in quiet compared to active sleep in newborns [Pihko et al, 2004].

KEY WORDS

Auditory evoked magnetic fields, Magnetoencephalography (MEG), Newborn, Sleep stages, Speech sound

INTRODUCTION

The capabilities of a newborn to discriminate changes in a stream of auditory information have been studied extensively with evoked potentials. Recently there have also been attempts to use magnetoencephalography (MEG) for studying brain functioning in newborns. So far there are only two studies on auditory evoked magnetic fields in newborns, the first one showing responses to a repeated tone [Lengle et al, 2001] and the second one suggesting a cortical generation of the mismatch response already in newborns [Huotilainen et al, 2003]. The present study examined if the newborn brain detects a change within a speech stimulus, as has been shown for 6-year-old children [Pihko et al, submitted].

METHODS

The subjects were 18 healthy newborns from the Helsinki University Central Hospital maternity ward, measured while 1–4 days old. In 10 full-term babies (5 females) the measurements were successfully carried out both in active and quiet sleep stages and therefore only data from those subjects are included. The 1 min Apgar scores were 9, except in two cases 8. The study was approved by the Ethical Committee of Helsinki and Uusimaa. One of the parents of each baby signed an informed consent form.

Stimuli were syllables /su/ (standard 76 %) /so/ (deviant 12 %) and /sy/ (deviant 12%) presented in an oddball paradigm. The phoneme duration was 219 ms for the fricative /s/ and 152 ms for the following vowel with an overall duration of 371 ms. (For details about the preparation of the stimuli see Pihko et al, submitted). In the following, only responses to the standard /su/ syllables are statistically analyzed. Stimuli were presented with an inter-stimulus interval (ISI) of 1 s (from the beginning of one to the beginning of the next stimulus). Stimuli were delivered to the left, contralateral ear through a plastic tube and a soft earpiece.

MEG was recorded with a helmet-shaped device with 306 channels (of which 204 were gradiometers and 102 magnetometers; Elekta Neuromag Oy, Helsinki, Finland). The measuring helmet was in a 'supine' position and the baby was lying with the right hemisphere downwards over the 'occipital' part of the helmet. Data were collected with a bandpass filter of 0.1–200 Hz using a sampling rate of 600 Hz.

Sleep stages were monitored via three EEG electrodes (F4, P4 and Cz) and two electro-oculograms, one on the upper left and the other on the lower right corner of the eyes. In addition, behavior of the baby (e.g., breathing pattern) during the measurement was monitored and coded on-line to the data file.

The data were averaged off-line according to the sleep stages. For statistical analysis, vector sums of the responses on the gradiometer channels were calculated with a low-pass filter of 40 Hz. From the vector sums, two amplitude averages were chosen individually, one 50 ms-long corresponding to the first, P1m peak, and a second, 100 ms-long corresponding to the second, P2m peak. For each subject, an average of vector sums from three channels with the maximal responses was used for ANOVA.

RESULTS

Figure 1 shows responses of one newborn (upper traces) and of one 6-year-old child (lower traces) to /su/ as a standard (continuous line) and /sy/ as a deviant (dashed line). The data from the 6-year-old was measured with the same paradigm and stimuli, but the child was awake and the ISI was 700 ms. In most newborns, a clear response to standards could be elicited in quiet sleep. The response consisted of a wider deflection, which in many cases showed separate peaks corresponding to the P1m and P2m of the response waveform of older children. In Figure 1, upper trace, the two peaks are clearly seen in the response to the deviant. Also after P1m and P2m, the waveform of the deviant response remarkably follows that of the older child with a deflection of opposite direction corresponding to a mismatch

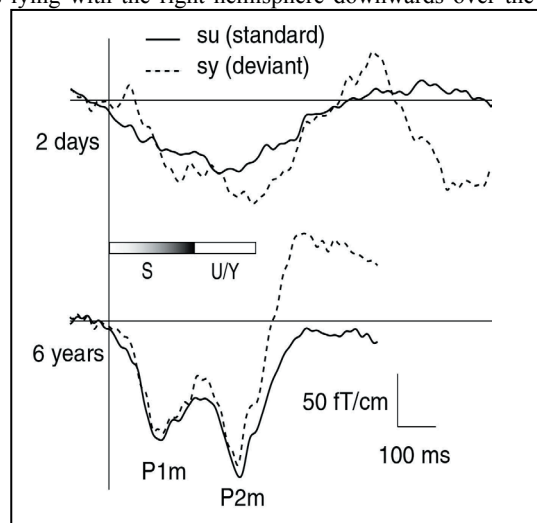


Figure 1. Auditory evoked responses to standard /su/ and deviant /sy/ measured from one newborn (upper traces) and a 6-year-old child (lower traces).

response. The average latency of the responses tended to be longer in newborns (190 and 435 ms) than in children (150 and 350 ms).

In active sleep, the responses to standards were generally smaller and not always distinguishable from the baseline activity. Figure 2 shows, on one gradiometer channel, grand average responses from the ten subjects measured over a contralateral location. 2-way ANOVA resulted in a main effect of the sleep stage [$F(1,9) = 36,5; p < 0,0002$], and a main effect of the peak [$F(1,9) = 7,7; p < 0,022$] with bigger responses in quiet than in active sleep and bigger responses during the second than during the first peak. In addition, there was an interaction of peak and sleep stage (Sleep stage 2 x Peak 2) [$F(1,9) = 6,4; p < 0,033$] indicating that the P2m was more enhanced than the P1m in quiet sleep.

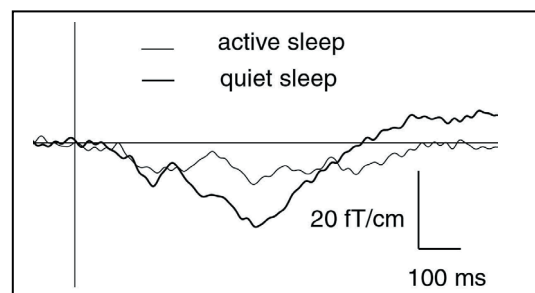


Figure 2. Grand average auditory evoked magnetic responses of newborns ($n = 10$) to the syllable /su/ in active (gray line) and quiet (black line) sleep stages.

DISCUSSION

Magnetic fields evoked by a speech sound in newborns in the present study are in agreement with a positive deflection measured in numerous evoked potential studies on fullterm newborns. This response is usually a broad deflection peaking around 300 ms. In our study, however, two distinct peaks were observed suggesting a contribution from the change within the stimulus. The two-peaked structure can be seen in responses evoked by /kaa/ and /ka/ stimuli in the study by Leppänen et al [1999], but with a shorter latency for

the 2nd peak (300–350 ms), presumably because of a shorter duration for the voiceless /k/ consonant.

The present study thus suggests that already a newborn reacts to different features within an auditory speech stimulus, namely those involved in a transition from a fricative to a vowel. In adults, onset of a word beginning with a fricative elicits a N100m response, followed by a N100m' triggered by the switch to a vowel [Kaukoranta et al, 1987]. In 6-year-old children the response to syllables /su/ and /sy/ consists of P1m and P2m, two deflections with opposite field distribution to those in adults (Figure 1. and [Pihko et al, submitted]), which is in agreement with developmental changes of auditory responses reported in EEG and MEG studies in children [Paetau et al, 1995][Ponton et al, 2000]. A similar sequence of N100m-N100m' can be evoked by a stimulus in which a noise burst is followed by a square-wave [Mäkelä et al, 1988]. The evoked magnetic responses to this mimicked fricative-vowel combination are diminished in dyslexic subjects [Renvall and Hari, 2002], adding thus a special interest to this stimulus combination in studies of young infants at-risk *e.g.* for dyslexia.

The ISI in the study with children was 700 ms while for the newborns it was 1 s. Longer ISI and analysis window were used to be able to record the later response. Longer latencies and less pronounced deflections of the newborns' responses reflect the relative immaturity of their brain.

Responses measured in quiet sleep were significantly larger than responses in active sleep. The effect of sleep stages to auditory evoked potentials of newborns have been shown earlier [*e.g.*, Ellingson et al, 1974], though there are studies reporting no effect [Cheour et al, 2002]. The sleep stage effect is also very clear for somatosensory magnetic fields in newborns [Pihko et al, 2004]. Given the pronounced sleep stage effect on the amplitudes of evoked magnetic fields, monitoring them is especially important in possible future experiments when clinical or at-risk groups will be studied and compared to control subjects.

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Cleaning Fetal MEG Using a Beamformer Search for the Optimal Forward Model

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ABSTRACT

We present a new method for improving the SNR of event-related fetal MEG signals based upon the SAM minimum-variance beamformer. SAM could separate the evoked response source activity from the remaining fMEG signal and interference if the evoked response source coordinates and forward model were known. However, this requires knowledge of both the coordinate of the evoked response source and its forward model. In late gestation, the vernix caseosa effectively insulates the fetus from the amniotic fluid. Hence, the forward model could be approximated by an equivalent current dipole in a homogeneously conducting sphere with its origin at the center of the fetal head. In the absence of accurate anatomical data, a beamformer could be used to evaluate all feasible source-origin combinations – selecting the combination giving the best signal-to-noise ratio (SNR) for the evoked response. Application of this approach to measured fMEG data reveals that the optimal model sphere location is described not by a single local sphere origin, but rather by all origins lying within an extended region. This result is explained by model predictions showing the same region of ambiguity [Vrba, 2004]. Although the model search does not localize the sources of the fetal evoked response, it does significantly improve SNR. This was demonstrated by analysis of fetal auditory evoked response data.

KEY WORDS

Fetal MEG, source modeling, minimum-variance beamformer, artifact reduction.

INTRODUCTION

A typical maternal MCG QRS complex has a peak vector magnitude of 120 pT. During the last trimester, the vector magnitude of the fetal MCG can be as high as 15 pT, depending upon gestational age and fetal orientation. These MCG artifacts are readily removed by orthogonal projection, with minimal attenuation of the remaining signal [Robinson, 2002]. Although orthogonal projection is sufficient for obtaining a clean unaveraged signal, the averaged evoked response is generally still too noisy to accurately determine peak latency and amplitude. The burst-suppression patterns appearing in unaveraged fetal MEG after cleaning have a peak amplitude of about 500 fT; that of the averaged evoked response is generally less than 50 fT. It follows that even were there no MCG artifacts, the SNR of the evoked response would still be close to unity after averaging 100 trials. In other words, the dominant interference to fetal evoked response studies is the unrelated fetal brain activity.

If a suitable forward model were available, together with the coordinates of the fetal brain center responding to the stimulus, one could separate the evoked response signal from all other interference, including unwanted brain activity, using a spatially-selective filter based upon the minimum-variance beamformer [Robinson, 1999]. In fact, this beamformer can be thought of as a form of “spatially-selective noise reduction.” During the last trimester, the fetal skin is covered by a secretion called the *vernix caseosa*. The *vernix* is a waxy material with low electrical conductivity. This layer should limit the volume currents due to fetal brain activity to the interior of the fetal head. Thus, one could approximate the forward model for the fetal MEG using a homogeneously-conducting sphere bounded by the fetal skin. In the absence of accurate anatomical coordinates, the beamformer method will attenuate all signals – including that of the evoked response. In this study, we have applied the SAM beamformer to perform a search for the optimal model maximizing the SNR of the evoked response. That model can then be applied to enhancing the evoked response waveform for more reliable characterization of fetal brain activity.

METHODS

The beamformer search method was implemented using these assumptions: Let the source forward model be a single current dipole in a homogeneously conducting sphere. The dipole source is located within a spherical shell with inner and outer radius defined to approximate the size of a fetal head and cortical layer thickness (including sulci). The location of the source dipole is unknown, relative to the origin of the spherical shell. To account for all possible source positions, we allow the dipole to be positioned at any point on a regular three-dimensional grid within the shell. Similarly, the local sphere origin is also unknown. We allow the source shell origin, to be translated to any point on a regular three dimensional grid within a rectangular region of interest, inside the maternal abdomen. This model is illustrated in Figure 1.

The model search is performed by evaluating the signal-to-noise ratio (SNR) of the averaged evoked response for each dipole source position within the shell. The source position giving the highest SNR is associated with its corresponding current local sphere origin. The entire source model is then moved to the next origin on the source model grid, and the process repeated until all model origins have been evaluated. The result is a three-dimensional functional map giving the best dipole source SNR as a function of local sphere origin. An example of such a map, relative to the primary sensor array, is shown in Figure 2.

Signal-to-noise ratio was evaluated by projecting the average and the $\pm$ average through the beamformer coefficients for each source/sphere-origin combination. This mapping function discriminates event-related activity from the background noise and clutter. It is identical to the

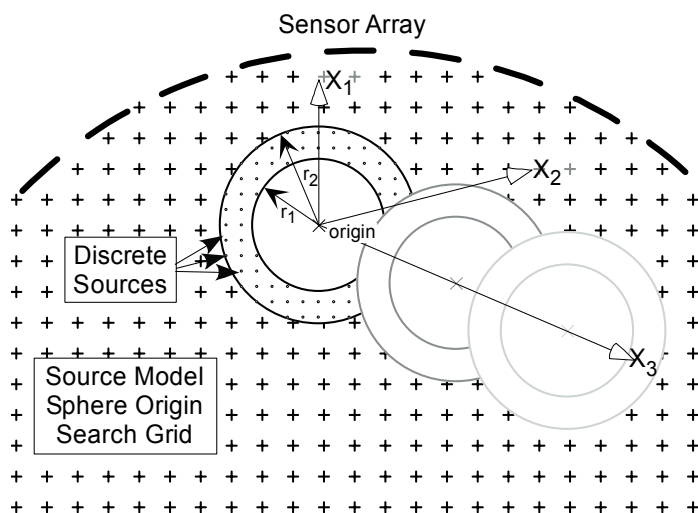


Figure 1. The source model for the fetal brain consists of a regular array of discrete sources within a spherical shell with inner and outer radius r_1 and r_2 , respectively. Volume currents are bounded at radius r_2 . Each of the sources is evaluated by minimum variance beamformer, and the entire model moved to each new origin on a regular grid.

function used for SAM localization of event-related activity in the adult, for which the sphere origin is known [Robinson, 2004].

This method was tested using fetal MEG data collected using an auditory evoked response protocol on the 151-channel SARA fMEG instrument. The mother (fetus gestational age 30 weeks) was seated with her abdomen resting over the sensor array. Three localization coils measured the positions of her abdomen relative to the sensor array; a fourth coil was used to mark the approximate location of the fetal head. Continuous data was acquired for 360 seconds in a passband of dc to 100 Hz (312.5 Hz sample rate). During collection, 100 trials of tone bursts were delivered to the maternal abdomen (nominal ISI of 3 seconds). A copy of the dataset was processed using orthogonal projection to attenuate fetal and maternal MCG, followed by signal averaging. The original data was analyzed using the beamformer model search – without prior cleanup of MCG artifacts. The model source shell had an inner and outer radius of 3.0 and 4.5 cm, respectively. The dipole source was evaluated on a three-dimensional 1 cm grid, bounded by these radii. The model local sphere origin was evaluated in 1 cm steps for a 20 x 19 x 22 cm region of interest. The SNR of the averaged evoked response source waveform (from the beamformer) was then compared with that resulting from orthogonal projection.

RESULTS

The beamformer search of the fMEG data yielded a spherical shell-like region of maximal SNR (Figure 2.). This region was located close to where the fetal head was marked on the mother's abdomen. A maximum SNR of approximately 5.9 was observed for this dataset. Using the best local source/origin combination found by the search, a SAM beamformer was used to compute the source waveform (i.e., virtual sensor) of the averaged signal. The averaged source waveform and its corresponding $\pm$ average are shown in Figure 3 (center traces). The evoked response can easily be seen, and is much larger than its $\pm$ average. By contrast, following orthogonal projection the average is no larger than its $\pm$ average (Figure 3, left traces). This demonstrates that the beamformer search improved SNR of the event-related activity. The evoked response cannot be seen without some form of artifact reduction (Figure 3, right traces).

DISCUSSION

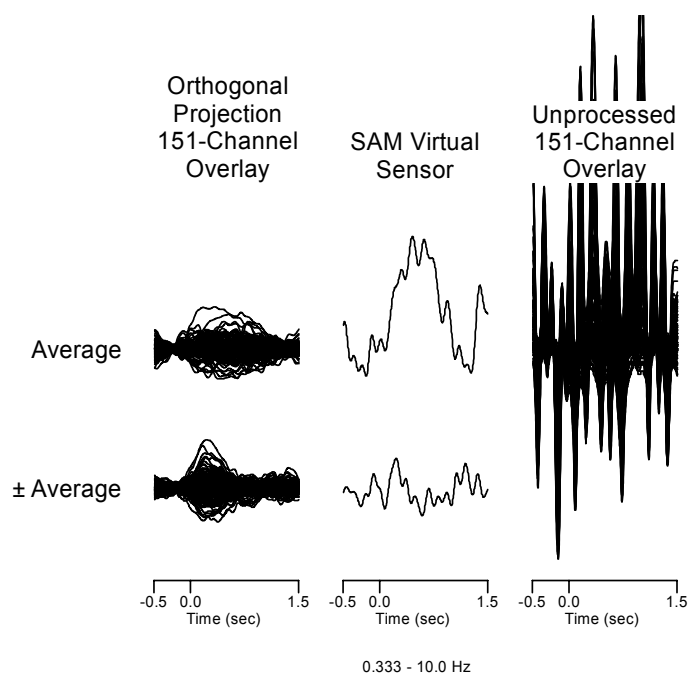


Figure 3. Comparison of evoked responses after signal averaging. Without artifact removal, the average of all sensors is dominated by interference from the maternal and fetal MCG ($\pm$ average not shown). Orthogonal projection attenuates the MCG artifacts, leaving an average that is dominated by outliers, as evidenced by the $\pm$ average being as large as the average. A SAM virtual sensor, based upon the results of the model search, reveals the event-related evoked response and strongly attenuates all other signals. As a result, the average is much larger than its corresponding $\pm$ average.

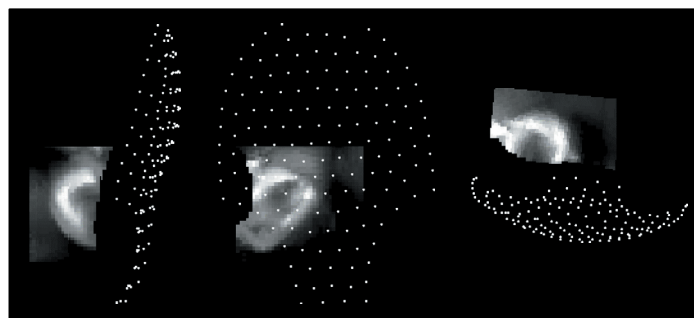


Figure 2. Image of maximum SAM SNR as a function of model sphere coordinate for event-related fetal MEG activity. The maxima (white) correspond to an SNR of approximately 5.9. The model search scan was performed at 1 cm intervals. The bright spherical shell shows the region of model ambiguity relative to the sensors. These results agree with theoretical predictions for multiple event-related sources. Dots indicate primary sensor positions for the 151-channel fMEG array. Note: This is not a functional source image!

Instead of there being only one best forward model, the beamformer search method found a shell-like region in for which all local sphere origins yielded approximately the same SNR for the evoked response. The resulting ambiguity agrees with predictions [Vrba, 2004]. This would be a problem were the purpose of the analysis to localize the fetal evoked response. However, the search method is intended to enhance the SNR of the fetal evoked response such that latency and response waveform morphology can be characterized. We have demonstrated that the method succeeds in improving the SNR – even when the interfering signals (MCG) are many orders of magnitude larger.

Despite the gain in SNR, the beamformer search method demonstrates conclusively that event-related activity is found within the maternal abdomen, close to the fetal head, but does not prove that this is due to fetal brain activity. Nonetheless, the evidence for the fetal evoked response is much stronger than with simpler artifact reduction algorithms. A search using a more sophisticated forward model could improve SNR even further.

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Fetal MCG and fetal MEG measurements with a 3-channel SQUID system

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ABSTRACT

Since the high costs of common large array SQUID system may hinder widespread application of fetal magnetoencephalography (fMEG) and magnetocardiography (fMCG), we intended to investigate a small non – commercial 3-channel SQUID system. The system comprises 3 axial first order gradiometers with 7 cm base length, 2 cm diameter and 2x2 windings of niobium wire, dc-SQUIDs (UJ-111), and current locked mode SQUID electronics that form an equal length triangle (22.5 mm). The system is mounted in a Cryostat BFH-7 model 16 with 5 mm “warm” – “cold” distance. System noise is about 10 fT/Hz^{1/2}. The fMEG and fMCG were recorded between 29 – 40 weeks of gestation after sonographic localization of the fetal head and heart using a 31-channel biomagnetometer (Philips) and the 3-channel-system, both in the same magnetically shielded room. The fMEG was recorded continuously over 500 sec (500 auditory stimuli, 100 dB SPL, 500 Hz, 50 ms, ISI 0.8–1.2 sec/ 1.6 – 2.4 sec, trigger channel, maternal ECG lead, sampling rate 1 kHz). The fMCG was recorded over a period of 5 minutes after dewar readjustment. The detection rates of cortical auditory evoked responses (CAER) reached 100 % for both systems. Cross confirmation of the components was difficult and may have uncovered false positive component detection. The fMCG was characterized by a systematic increase in SNR under application of the smaller device. The small size array provides a profitable alternative for the fetal applications.

KEY WORDS

Fetal magnetoencephalography, fetal magnetocardiography, SQUID, cortical auditory evoked responses (CAER), signal to noise ratio (SNR)

INTRODUCTION

Although measurement of fetal magnetocardiography (fMCG) and fetal magnetoencephalography (fMEG) has proven valuable for clinical diagnosis of fetal cardiac pathology [Kähler, 2001] [van Leeuwen, 1999] and in the investigation of fetal brain function, so far only very few centers have applied it [Eswaran, 2002] [Lengle, 2001]. Fetal biomagnetic studies, in particular fMEG, have ever since been limited by a low signal – to – noise ratio (SNR). Recording quality mainly depends on the distance between the sensors and the deep sources of the fetal biomagnetic signals. In addition, the uncertainty about a constant spatial relation between sensor and sources and the amount of disturbing biomagnetic activity from other sources than fetal reduce the SNR [Schneider, 2001]. Common large array multi-channel SQUID systems have in general been designed for other purposes than fMEG and fMCG. Their approximation to the abdominal wall of a woman pregnant in the third trimester is obviously anatomically limited. Two ways appear possible to go: either to design an array with a special shape for the particular purpose [Vrba, 2004] or to reduce the number of channels in order to minimize the dimensions of the dewar. The latter approach may suffice to answer most of the currently imaginable questions in fetal biomagnetism, although small devices are inadequate for high spatial resolution properties. Hence, we have developed and investigated a 3-channel SQUID system for fMCG and fMEG measurements and compared the results to a commercial multi – channel system intraindividually and in the same experimental setting.

METHODS

We used a 31 – channel – SQUID low temperature biomagnetometer [Philips^R] in all previous fetal biomagnetic studies. The system consists of 31 symmetric first order gradiometers with a coil diameter of 20 mm and a base length of 70 mm. The system is cooled by liquid helium and mounted in a dewar in a non – magnetic gantry. The sensors cover an area of 145 mm in diameter. The base of the dewar is curved in a concave manner. The intrinsic noise of this system is below 10 fT/Hz^{1/2} [Dössel, 1993].

The new system as well comprises axial first order gradiometers with 70 mm base length and 20 mm diameter. They are made of 2x2 windings of niobium wire (thickness 80 µm) [Philips^R], dc-SQUIDs (UJ-111), and current locked mode SQUID electronics. The 3 channels form an equal length triangle with a side length of 22.5 mm. The SQUIDs are based on thin film Nb-NbO_x-Pb/In/Au technology with two 3x3 µm² Josephson junctions. They are operated in current locked mode to eliminate crosstalk between the channels. For this purpose, the modulation and feedback currents are coupled into the flux transformer instead of the SQUID itself. To eliminate trapped flux, the SQUIDs can be heated by means of thick-film resistors. The SQUID system is mounted in a Cryostat BFH-7 model 16 with 5 mm “warm” – “cold” distance. The system noise is about 10 fT/ Hz^{1/2}.

Both systems were used consecutively in the same subjects in a standard magnetically shielded room Type Ak 3b [Vacuumschmelze Hanau^R]. A single fMEG recording consisted of 500 s of continuous SQUID signal, recorded without skin contact directly above the fetal head over the maternal abdomen. During that time auditory stimuli of 100 dB, 500 Hz and 50 ms tone length were applied to the maternal abdominal wall from an external sound generator via a 5 m plastic tube with an ISI of on average 1 or 2 sec respectively (randomly between 0.8–1.2/1.6 – 2.4 sec). The sampling rate was set at 1 kHz. Fetal MCG was recorded over a period of 5 minutes after readjustment of the dewar to the cardiac position. Each session consisted of 4 recordings of fetal MEG, 2 with each system, and 2 fetal MCG recordings.

Subjects were 10 women pregnant between 29 – 40 weeks of gestation. After informed written consent the subjects were positioned comfortably on a wooden bed inside the shielded room. The fetal baseline heart rate was determined over a period of 3 minutes and the positions of the fetal head and heart were recorded. The depth of the fetal head was checked upon to be less than 5 cm. After the preparation the dewar and sound applicator were positioned and the sessions performed as described above. Finally, the position of the fetal head was confirmed by ultrasound.

fMEG-data were pre-processed to remove maternal and fetal cardiomagnetic activity cycles. These were sequentially matched and averaged by a Maximum-Coherence-Matching algorithm. The template QRS complexes were taken from the maternal ECG or the fetal MCG trace with the highest SNR, respectively, and the number of fetal heart actions adjusted to baseline heart rate. The averaged signals were consecutively removed by time-exact subtraction from the raw data after implementation of a baseline-correction [Schneider, 2001]. The data underwent triggered averaging and software filtering (2.7-20 Hz), baseline correction and split half averaging analysis of the fetal cortical auditory evoked responses (CAER).

The fMCG was averaged using a fetal QRS complex as template without removing the maternal signals and after bandpass-Fourier-filtering the data from 0 to 100 Hz linear with a notch – filter at 50 ± 2.5 Hz to simulate a ‘worst – case – scenario’. The signal – to – noise ratio (SNR) was determined from the range of the baseline correction as provided by CURRYTM. The baseline was set in the PQ – interval [Grimm, 2003].

RESULTS

Detection rates of any CAER components in fMEG reached 100 % (10/10, 26 components 3-channel, 23 components 31-channel) with both systems. Singular components could be cross – confirmed with both systems in 8 out of 10 sessions. Nevertheless, on 7/17 occasions from 5/10 sessions, there were discrepancies in latency between both systems that suggest at least one false – positive detection (Table 1). 15 times a component could only be detected with one of the two systems (9x 3-channel/6x 31-channel). The best cross confirmation was observed for the P1pm ($\chi^2=0.625$, n.s.). While it was high for P3pm, especially by application of the small system the component could not be determined unequivocally.

Table 1

Detection	3-channel-system			31-channel-system			Cross -confirmed	
	Session	ISI 1 s	ISI 2 s	session	ISI 1 s	ISI 2 s	Yes	no
No. of subjects	10	10	8	10	10	8	10	10
overall	10	10	7	10	10	7	8/10	5/10
P1pm	6	5	2	4	4	1	3/3	0/3
P2pm	5	4	4	5	2	5	1/3	2/3
N2pm	7	4	3	4	4	1	2/3	1/3
P3pm	8	7	4	10	8	5	4/8	4/8

Data from 16 fMCG were available (intra-individual comparison in 8 subjects). The noise ranged from 13 to 55 fT/Hz^{-1/2} (mean 31.9) for the 31-channel and 19 to 81 fT/ Hz^{1/2} (mean 47.1) in the 3-channel system (p=0.006; paired t-test). A strong correlation between noise and SNR could only be confirmed in the small system (r= -0,868; p= 0,005; Pearson). In contrast to these findings, the mean SNR was higher with the smaller system (53 vs. 43, n.s., paired t-test). In all 16 recordings the SNR was higher than 10 without exception. Gestational age did not influence the level of noise. The number of matched QRS complexes was higher with the 31-channel system and, generally speaking, sub-optimal in fMCG standard quality terms.

DISCUSSION

The variety of influencing factors to fetal biomagnetic studies is vast and in experimental settings difficult to handle [Schneider, 2001]. During the last few years a steady learning curve has lead to increasing detection rates in fMEG under application of different recording systems and methods of processing and analysis [Lengle, 2001] [Eswaran, 2002] [Vrba, 2004]. The high initial detection rates in this study suggest that the learning curve has reached its upper end. Nevertheless, cross confirmation failed in one third of the occasions. Habituation to the stimuli, cephalic movement, incorrect sensor positioning especially of the smaller dewar or less critical handling of the signals on the brink of disappearance in the noise are possible explanations for inconsistencies mainly of the later components, that are less confined to the primary auditory cortex [Rotteveel, 1987]. A true advantage of a small-head system for the fMEG could not be elaborated in this small study. But it served as a valuable alternative buying off the lower distance to the source with a higher intrinsic noise level.

Taking into account the low level of signal pre-processing in this study, the fMCG data propose to use smaller channel numbers when source localisation is no issue (i.e. HRV analysis). The data fulfilled the agreed basic quality criteria for fMCG [Grimm, 2003], (Figure 1). The 31-channel-system has been more influenced by maternal cardiac activity which may find its expression in the higher SNR of the smaller system. Removal of maternal cardiac activity cycles may have levelled this difference. The authors considered the effort not worthwhile doing. Generally speaking, the 3-channel-system is more susceptible to movement artefacts in the heart rate traces. In order to generate a complete set of the NN-intervals some kind of smoothing filter will be unavoidable.

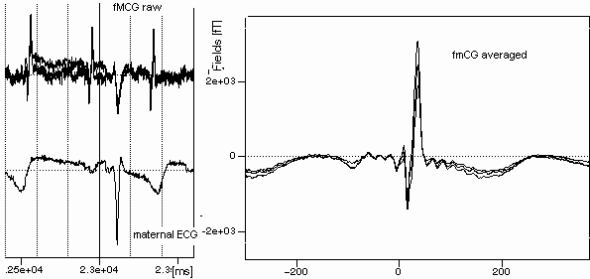


Figure 1

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Auditory magnetic mismatch negativity response in the human fetal brain

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The mismatch negativity response (MMN) to auditory stimuli allows the study of cognitive function of the human brain. MMN has been successfully recorded in newborns [1]. Apart from standard MMN, they also observed a late discriminative negativity response (LDN). The aim of our study was to investigate the capability of the fetal auditory system to recognize two different tone stimuli, using the oddball paradigm, to evoke a MMN response. The recordings of weak magnetic fields from the fetal brain was performed with the 151 channel MEG system called SARA (SQUID Array for Reproductive Assessment). Two tone bursts were presented in a sequence of a standard tone of 500Hz intermixed with a deviant tone of 750Hz in 12 % of the stimulus, with an inter-stimulus interval of 800ms. The stimuli intensity delivered over the maternal abdomen was 110 dB. Nine subjects were investigated serially (every two weeks) starting at 28 weeks of gestation. Fetal and maternal heart signals were attenuated by signal space projection method. The averaged evoked responses for standard and deviant tone was obtained (100 ms pretrigger, 600 ms posttrigger) and then MMN response was calculated. Detectable MMN responses were obtained in 70 % of the investigated fetuses at different gestational ages. In 3 of the patients, the MMN response from the fetal brain was obtained as early as 28 weeks of gestation. In 80 % of the cases with successful recordings, an additional late response component was observed. The response latency of all components showed a decreasing trend with an increase in gestational age. In conclusion, the magnetic MMN response from the fetal brain was successfully recorded starting at 28 weeks of gestation. Further MMN response studies could contribute significantly to better understanding of fetal learning.

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Tracking developmental changes in the visual evoked responses in human fetus using MEG

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In this study we present results of VER recordings in human fetuses starting at 28 weeks of gestation performed using a 151-channel MEG system called SARA (SQUID Array for Reproductive Assessment). A flash stimulus was used to elicit the visual evoked response. A total of 31 studies were performed on 12 subjects at different stages of gestation ranging from 28 to 40 weeks. Prior to the MEG measurements an ultrasound was performed on all the fetuses. Each recording session lasted for 6 minutes and consisted of approximately 180 flashes. Interfering maternal and fetal heart signal components were removed by applying a spatial-filter based projection algorithm. Stimulus triggered averaging was performed (0.2 s pre-stimulus and 0.8 s post-stimulus). The results were bandpass filtered between 0.5-10 Hz. A simple classification scheme was adopted based on the latency values recorded for flash VER's on preterm infants. The peaks with latency <300 ms were labeled as fetal P200 (fP200) and with latency values > 300 ms as fetal P300 (fP300). 18 of the 31 recordings showed a discernible response. The average fP200 latency in each of three gestation age groups were - 28-32 week : 248.6 ms ; 32-36 week - 196.2 ms ; 36-40 week : 115 ms. Correlation analysis showed a significant decrease of fP200 latency with increasing gestation ($r = -0.79$, $P < 0.05$). The average fP300 latencies in the three groups were 366 ms, 340 ms and 368 ms respectively and no significant trend was found over gestation. In conclusion, the progressive decrease in fP200 latency may reflect the different stages in the physiological development of the visual pathway. VERs recorded using MEG could become a beneficial tool to detect the functional abnormalities in the brain development of at least the severely neurologically damaged fetus.

3D Ultrasound Images for Realistic Volume Conductor Modeling of the Fetal MEG

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The aim of this work is to develop a source localization scheme for fetal magnetoencephalography (fMEG) in order to verify the origin of the auditory evoked fields recorded above the maternal abdomen [1]. Here, we present the construction of realistic volume conductors based on 3D ultrasound images and numerical simulations of the fMEG. 3D Ultrasound images were obtained from 4 healthy pregnancies with the help of a 3D extension (TomTec Imaging GmbH, München, Germany) mounted to a commercial ultrasound device (Nemio, Toshiba, Japan). The 3D extension adds to the 2D stream of images 3D coordinates and orientations with the help of a magnetic positioning system attached to the ultrasound probe. Software developed at the Biomagnetic Center converts these images into a data set comparable to 3D MRI data for the purpose of import into the source localization software Curry (Neuroscan, USA). The conversion also includes the adjustment of the curvature of the maternal abdomen and, if necessary, image manipulation (e.g. gray scale correction). After the import into Curry segmentation of the fetus was performed and a triangulated surface for the fetus and the maternal abdomen was constructed. From these surfaces we developed a realistic volume conductor model of the maternal abdomen and the fetus. Forward simulations were performed with a single dipole placed into the head of the fetus. The results of the simulations are in good agreement with the measured fMEG field maps.

This work was supported in part by the German Ministry of Science.

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Development of Neonatal Auditory Evoked Responses

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We have evaluated auditory evoked responses to brief 1kHz tones in neonates ranging in age from 1-24 weeks. The data was collected in long, continuous runs with a floor-standing 37-channel sensor (MagneS, 4D Neuroimaging). The recordings were scored for sleep state by classifying them as high frequency/low amplitude (active), mixed frequency, or low frequency/high amplitude (quiet) sleep. For each state, averaged responses were computed using a signal-processing algorithm described elsewhere [1]. Previous EEG auditory studies, such as [2], delineated the P250, N500 and P750 as characteristic components in the age range of our data that decrease in latency with increasing CA. Analysis of our data suggests an early (0-6 week) neonatal auditory response characterized by monophasic waveforms with a distinct P250 amplitude peak. During a subsequent transition period (6-10 week), the emergence of weaker responses at about 600 and 850 msec produce a more complicated waveform morphology. The P250 exhibits a decrease in latency and increase in amplitude with increased age. After 10-12 weeks, a small 150 msec component is seen. Generally, few sleep state differences are observed; however, after 12 weeks the components around 250 msec have distinct morphologies in mixed frequency versus quiet sleep. Our results suggest a significant transition period at 6-12 weeks.

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Somatosensory evoked magnetic fields to median nerve stimulation in newborns

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We studied somatosensory evoked magnetic fields (SEFs) to electric and tactile stimulation in newborns. The electric stimulation was applied to the left median nerve at the wrist, and the tactile stimulation to the tip of the left or right index finger by movement of a plastic membrane touching the skin. An interstimulus interval of two seconds was used. The evoked magnetic fields were measured over the right hemisphere with a 306-channel MEG-system (Elekta Neuromag, Oy). The data were off-line analyzed for active and quiet sleep stages. The first deflection after the median nerve stimulation, N1m, corresponding to the adult N20m, peaked at about 30 ms. During this early peak, the field pattern was dipolar and the activity could be modeled using an equivalent current dipole (ECD). The coordinates of the ECD were in agreement with activity generated at the somatosensory cortex, the current dipole pointing anteriorly. The locations of the later deflections were compared to the origin of N1m. After the tactile stimulation, P1m with a latency of about 70 ms was present for the contralateral, but not for the ipsilateral stimulation, suggesting the possible origin of the P1m at the primary somatosensory cortex. We conclude that the early SEFs to electric stimulation of the median nerve from the primary somatosensory cortex can be detected and modeled by ECDs already in newborns.

Effects of antenatal glucocorticoids (GC) on parameters of human maternal and fetal cortical function detected by simultaneous registration of maternal EEG and fetal MEG

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Objectives: Antenatal GC alter brain function in fetal sheep. Based on our experience in fMEG we investigated the effects of GC administered to pregnant women on fetal and maternal brain function by analyzing responses to auditory evoked reactions (AER) and spectral and nonlinear analysis of the electrocortical background activity in fetal MEG and maternal EEG. **Methods:** 10 pregnant women at 30 to 35 weeks of gestation threatened by premature labor were treated with 12 mg betamethasone (BM) i.m. on two consecutive days. fMEG was performed with a 31-channel-SQUID-biomagnetometer (Philips) during two alternating 250sec periods of rest and acoustic stimulation (500 Hz, 100 dB applied at the maternal abdominal wall, 50 ms duration with randomly chosen inter-stimuli intervals of 0.8–1.2sec) prior to the first (control) and 2–6 h after second BM injection. A maternal nine channel EEG (Cz, F3/4, T3/4, P3/4, O2/3) was simultaneously recorded (sampling rate 1 kHz). **Results:** AER could be detected in all fetuses. BM induced a latency shift of P2pm component from 180±5 to 192±8 ms ($p<0.05$). In maternal EEG the P2 peak latency was also delayed from 163±5 to 179±6 ms and the P2 amplitude increased ($p<0.05$). BM decreased the EEG beta activity ($p<0.05$) and complexity ($p<0.05$) of maternal cortical activation. Alpha, delta and theta activity was not affected. **Conclusions:** Antenatal GC therapy to enhance fetal lung maturation affects fetal and maternal brain function. The decrease of the EEG beta activity and complexity and the delay of the P2 latency are indicative for disturbed neuronal interactions.

Sixty-Four Channel MCG and Three-Dimensional Current Density Maps

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ABSTRACT

The magnetocardiography (MCG) is characteristic of three dimensional (3D) measurement of cardiac disorders. We have developed a new prototype 64-channel MCG system. The aim of this study is to develop a 3D current density map (CDM) for the visualization of 3D cardiac outline. Our MCG system consists of 64 first-order gradiometers and analogous FLL. We used modified minimum-norm method with Tikhonov's regularization for calculating space filter. We analyzed magnetic field data in 20 healthy volunteers. In a shielded room, we obtained the B_z magnetic component of the 64-channel simultaneous data. The 3D CDM in the section of P and QRS waves were calculated by integrated magnetic data after applying the space filter. In addition, we generated the series of paths of 3D current density of atrial and ventricular conduction, superimposed on the 3D CDM. Furthermore, magnetic resonance (MR) image were obtained in three volunteers, and CDM were reconstructed on the MR images. The 3D CDM in the P and QRS section corresponded with the cardiac silhouette in three volunteers. We also measured magnetic signals due to currents in five coils as a simple phantom.

In conclusion, 3D CDM may be useful for visualizing cardiac disorders.

KEY WORDS

magnetocardiogram, cardiac modeling, current density

INTRODUCTION

The magnetocardiography (MCG) measurement is a non-invasive method for estimating the current source. It has been applied to the examination of an anomalous conduction pathway in WPW syndrome. However, it is difficult to get an inverse solution when the source is wide spread.

We have developed visualizing and analyzing method of heart-current using MCG measurement. We have demonstrated the three dimensional current density map (3D CDM) using a space filter [K. Nakai 2002, M. Yoshizawa 2002]. The purpose of this study is to examine 3D CDM reconstructed on the magnetic resonance (MR) images.

METHODS

The magnetocardiogram and the magnetic resonance images were measured using these equipments.

- MCG
64-channels MCG (Iwate Medical University)
Observation Area : 175 mm × 175 mm (show in Figure 1.)
- SQUID sensor
Low-Tc-dc-SQUID 1st-order Gradiometer
(HITACHI High-Technologies. Co., ltd.)
- 64-channels Flux Locked Loop circuits
- Measurement condition
In the magnetic shielding room (Parmaroy-Aluminium-Parmaroy)
- MRI
GE SIGNA HORIZON 1.5 (Iwate Medical University)

Sixty-four-channels MCG and 1-channel electrocardiogram (ECG) were recorded approximately 600 heart beats. MCG were averaged by triggered R wave peaks of ECG. The 3D CDM was calculated in the section of P and QRS waves by integrated current density data after applying the space filter.

RESULTS AND DISCUSSION

The 3D CDM superimposed on the MR image :

We constructed the 3D CDM on three healthy volunteers (A ; age 35, B ; age 35, C ; age 45). Figure 2 shows 64-wave forms and integral section at P and QRS waves. The 3D CDMs superimposed on the MRI showed in Figure 3. The 3D CDM reflected their cardiac silhouette.

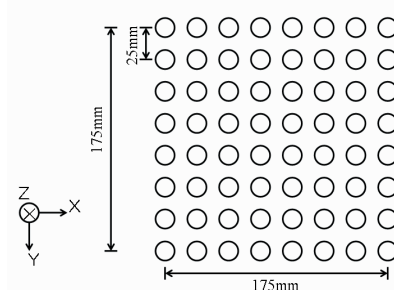


Figure 1: SQUID sensors prepared 8×8 array in 64-channels MCG

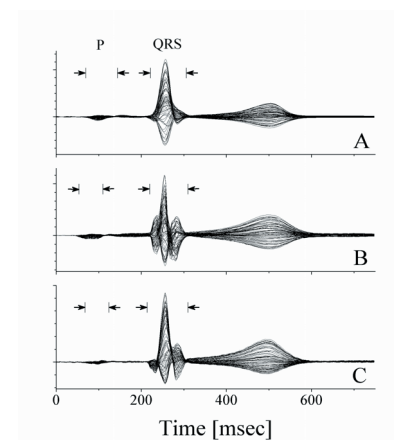


Figure 2 : MCG wave forms and integral sections.
A : P; 70~144 msec, QRS; 222~306 msec
B : P; 54~110 msec, QRS; 220~310 msec
C : P; 68~124 msec, QRS; 214~310 msec

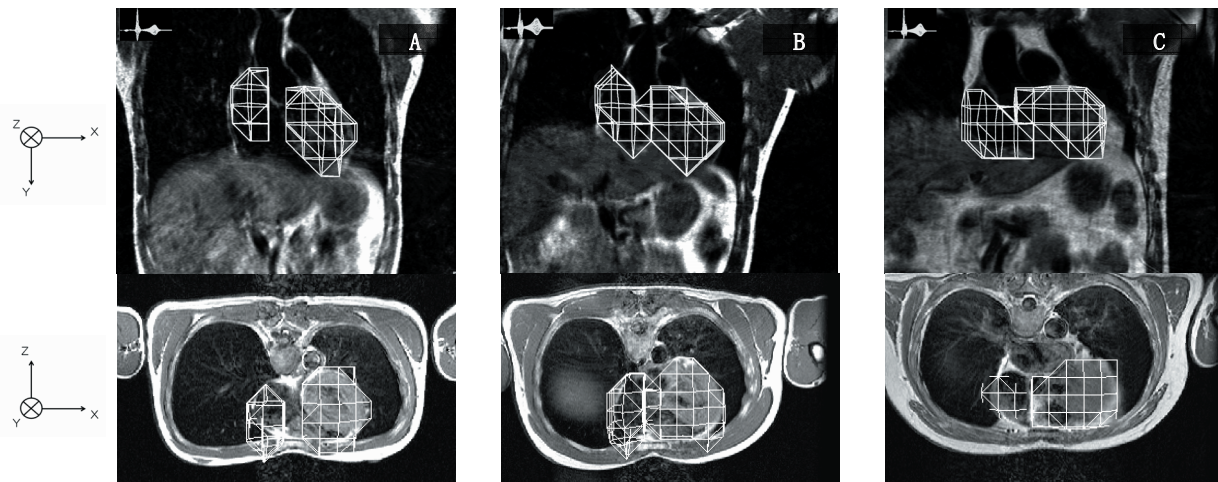


Figure 3 : The 3D CDM reconstructed on the MR image.

Experimental using Cu coils :

We generated a phantom consider of five Cu coils for measuring current density (Figure 4). A short current pulse was fed to each coil, and magnetic signals from these coils were measured by 64-channels MCG. The 3D CDM of RING I was constructed at $z = 42 \sim 77$ mm and its diameter $\phi = 52.5 \sim 105$ mm. RING IV was constructed at $z = 59.5 \sim 112$ mm and its diameter $\phi = 70 \sim 122.5$ mm [Table 1]. This results explicated to the focus gap on the magnetometer as $\delta x = z/\sqrt{3}$ for inplane direction and $\delta z = z/6$ for Z direction. RING I focused $\Delta\phi = 5 \sim 47.5$ mm and $\Delta z = 13 \sim 22$ mm, RING IV focused $\Delta\phi = 22.5 \sim 30$ mm and $\Delta z = 4.5 \sim 48$ mm. On the gradiometer, it will lead small range than the magnetometer. And the focusing range in the 3D CDMs estimated less than δx and δz with error range that depends on voxel size.

Figure 5 and 6 show the results of the 3D CDM using double pulse current was input to RING I and IV. The 3D CDMs of different sources were separated spatially.

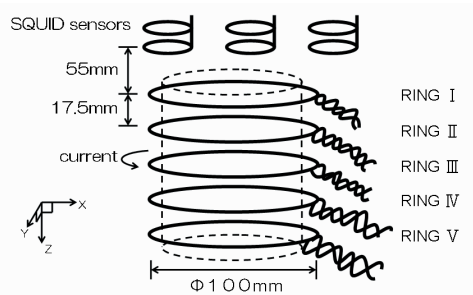


Figure 4 : Experimental setup of phantom coil.

	z	Δz	$\Delta\phi$	δz	δx
RING I	55	13~22	5~47.5	9.2	31.8
RING II	72.5	13~22	5~47.5	12.1	41.9
RING III	90	4.5~30.5	5~30	15.0	52.0
RING IV	107.5	4.5~48	22.5~30	17.9	62.1
RING V	125	22~48	12.5~75	20.8	72.2

Table 1 : Focus ranges of five Cu coils. ([mm])
 z ; distance from measurement surface to Cu coils.
 $\Delta z, \Delta\phi$; focus range of Z and diameter, readout from the 3D CDM.
 δx ; $\delta x = z/\sqrt{3}$. δz ; $\delta z = z/6$.

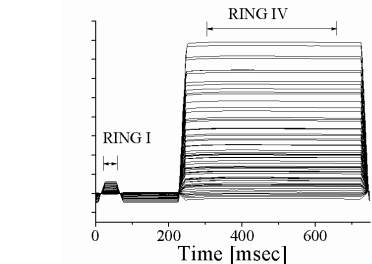


Figure 5 :Pulse signal wave forms and integral sections.

CONCLUSIONS

This phantom experiment gave a possibility to visualize atrial and ventricular by 3D current density non-invasively.

ACKNOWLEDGEMENTS

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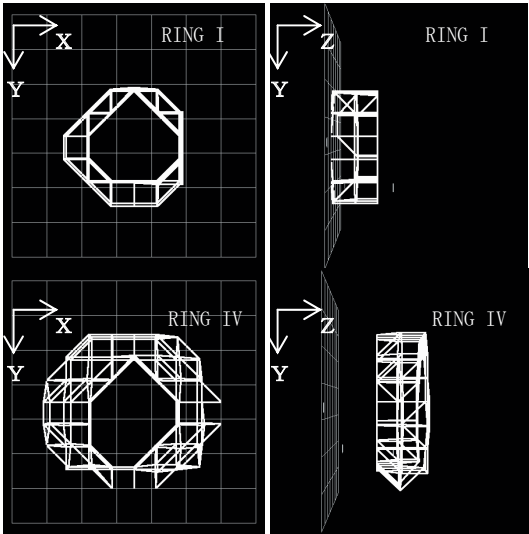


Figure 6 : The 3D CDM of RING I and RING IV. The lattice line shows the SQUID sensor arrangement.

The MCG Torso Model Study of Current Flow Heterogeneity

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ABSTRACT

The goal of this study was to investigate the extent to which electrical heterogeneities could be demonstrated to affect the electric potential signals (EPS) differently from the current density distribution as reconstructed from the MCG. A simple physical human torso was constructed in which discrete but different electrochemical sources could be activated with a current flow of a characteristic shape and duration. Simultaneous recording of the MCG and ECG was then carried out and the results compared. The present study adds a new element of understanding of the ion cellular basis of the heterogeneity manifestation by showing that experimentally induced current flow with different regional duration and position can create characteristic magnetic signals in some cases without visual changes on EPS.

KEY WORDS : Magnetocardiogram , Ischemia, Current Density Heterogeneity, Electrical Sources.

INTRODUCTION

During cardiac repolarization – the ST-T segment – its magnetic field as well as the surface electrode derived ECG, are based on events taking place at cellular level at multiple sites in the myocardium. Yet differences in the mode of charge transport and in the current anatomical structure relationships may affect the MCG, reconstructed from current density distribution (CDD), in a different way than is the ECG, derived from surface electrodes. In particular, inhomogeneities in the cardiac muscle may affect the magnetic field such that they may be detected by the MCG whereas the voltage measurements from the ECG may not do so.

The goal of this study was to investigate the extent to which electrical heterogeneities could be demonstrated to affect the electric potential signals (EPS) differently from the current density distribution as reconstructed from the MCG.

METHODS

An extended physical source model (SM) suitable for magnetic measurements was constructed by layers of discrete electrical cells with a total dimension of 50mm x 15mm x 15mm, as shown in figure 1b. Each “cell” consists of a small electrochemical battery, with the negative electrode directly connected to an exterior copper electrode and the positive one connected through an electronic key to the other exterior copper electrode on the opposite side of the phantom torso.

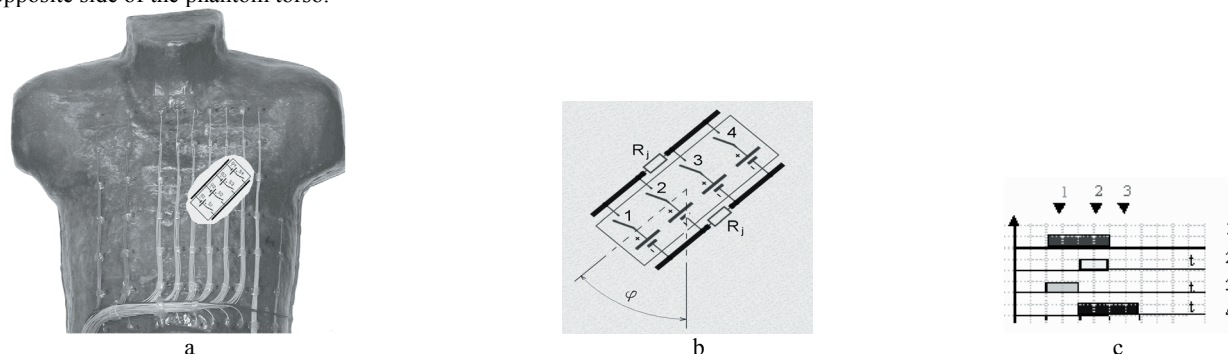


Figure 1. The torso model (a) , the electric circuit of a source of a field (b) and the diagram to switch on the keys(c).

The “cells” are electronically coupled as a “multicellular” layer through coupling resistances R_j and copper electrodes and are subject to electronic interaction. The cells were covered and carefully isolated by epoxy resin, so that no fluid could leak. The source model was assumed to be located in a homogeneous volume conductor in an anatomically realistic torso model of an adult male subject, as depicted in Figure 1a. The torso model was filled with a 0.9% saline solution. The external copper electrodes were connected to it. Each discrete cell had a characteristic current flow duration colour-marked in Figure 1c in the cell 1, the cell 2, the cell 3, the cell 4 and electrode direction assigned to it.

The SM behaves as a set of electrical sources and the coupling resistance that generate a potential in the surrounding volume conductor. The SM voltage gradient that develops as a result of the imposition of a current sources layer in the “heart” region of the torso model plays a dominant role in the production of EPS. The currents inside the SM can be interpreted as an impressed (i.e. applied) current. In order to simulate a shift in the position of ion currents, the potential impulses of a rectangular shape were supplied with different durations to the key electrodes with a frequency of 1.0 Hz. The model study allows comparison with real experiment only in the order of magnitude. The absolute values of the resistivity are less important than other simplifications used. Measurements were obtained with a 4 channel system (MCG-7®, MagScan GmbH Essen, Germany) in an unshielded setting. CDD maps were plotted by the method of the “inverse problem solution” [Primin,1999]. The currents flowing through the phantom volume created potential differences on the phantom body surface which were displayed as EPS. These data were acquired by a commercially available electrocardiograph simultaneous with the recording of the magnetic signals.

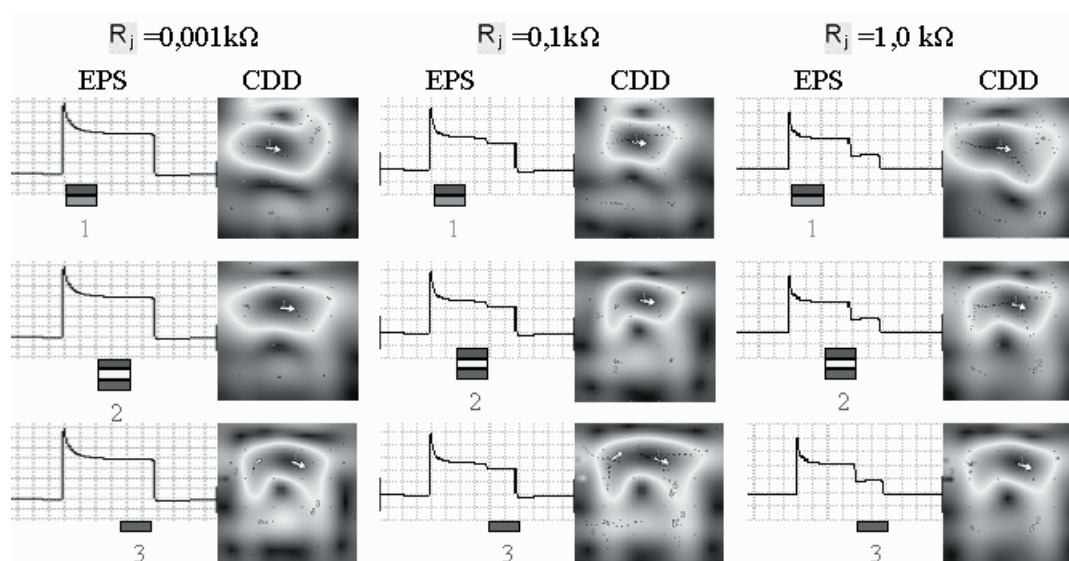


Figure 2: CDD maps at the time moment of the cells activity marked by the cursors 1,2,3 for three different R_j values.

RESULTS

Figure 2 displays an examples of the reconstructed CDD in a frontal view for current sources (cells) at their pre-set location as well as the corresponding EPS time course. No significant difference is visible on EPS during activation of the different cells at $R_j=0,001 \text{ k}\Omega$. Where as clearly different CDD pictures are obtained by MCG measurement. With increasing R_j , a difference even in the EPS appears.

DISCUSSION

The present study adds a new element of understanding of the ion cellular basis of the current heterogeneity manifestation by showing that experimentally induced current flow with different regional duration and position can create characteristic magnetic signals in some cases without visual changes on EPS, although changes in resistivity (R_j) are reflected while the CDD maps remain virtually the same (compare left hand panel with right hand panel in figure 2). In our model study only a two-dimensional reconstruction was carried out, whereas in reality current flow is three-dimensional at various depths. If we assume that the resistance R_j is a simplified model of a cardiac conductor conductivity or of gap junction coupling, our study highlights the important influence of the extent of gap junction coupling on the manifestation of the current flow heterogeneity in multicellular tissue. [Montague,1989] considered that myocardial ischemia is a biologically heterogenous process that may begin with biochemical changes and [Carmeliet,1999] demonstrated that during ischemia the dissociation between the very early changes in the transmembrane action potential and the more delayed electrical cell-to-cell (un)coupling is quite prominent.

Following the line of thought, as [Hailer ,1999] stated , that increased heterogeneity of repolarization can be considered an early sign of ischemia and “ other available methods used to detect ischemia might not be an appropriate reference method” we conclude that the basic clinical advantages of the MCG-technology is its ability to detect the current heterogeneity changes in ischemia earlier than it could be displayed in electric potential signals by ECG. The result of this study now helps to understand why a lot of MCG studies show a ability to earlier detect myocardial ishemia compared to ECG.

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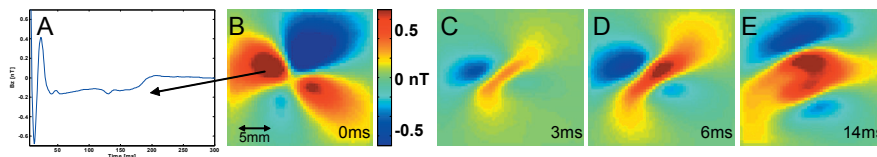
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Combined high resolution MCG and action potential imaging

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The heart's magnetic field is exquisitely sensitive to anisotropy ratios in the cardiac bidomain model; Therefore, magnetic imaging of cardiac action currents is an ideally suited technique for testing the accuracy of cardiac models and elucidating the effects of anisotropy in the spread of stimulus and action currents. We mapped the magnetocardiogram (MCG) as a function of position over a 1cm^2 area of the left ventricle of a Langendorff perfused isolated rabbit heart using high-resolution scanning SQUID microscopy and epi-fluorescent imaging with a high speed CCD camera and the transmembrane voltage sensitive dye di-4-ANEPPS. The combination of these two methods allowed us to map the transmembrane potential, V_m , the magnetic field, and consequently the total current, over the same area. The MCGs (A) were combined to produce a time series of 2D field maps that show a clear octopolar pattern during the cathodal current injection (B), a similar pattern with a reversal of currents immediately after terminating the stimulus (C), and the generation and propagation of an elliptical action current wave front (D,E). The observed patterns are in agreement with predictions using a bidomain model. Our high-resolution SQUID images have confirmed that unequal anisotropies in the intra- and extracellular spaces must be considered to explain the magnetic field associated with action current propagation. However, a realistic cardiac bidomain model incorporating fiber rotation, cleavage planes, and tissue heterogeneities are required to reproduce the complete experimental observations.



Magnetocardiographic Gradient Analysis of Atrial Activation

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A pseudo-current pattern reflecting the bioelectric currents in the heart can be obtained from multichannel magnetocardiographic (MCG) data without needing to apply specific source and volume-conductor models. The method is based on estimating the gradients along the sensor-array surface from the magnetic-field component perpendicular to the chest (B_z) [1]. The largest surface gradient in the sensor array reveals the site of the active region, while the direction of the gradient provides a useful tool for analyzing the cardiac activation sequence. Dipolar currents produce one clear gradient amplitude maximum and a unidirectional pseudo-current pattern, whereas rotating gradients and multiple amplitude maxima refer to multidirectional currents in the heart. The method was applied to study atrial activation of two different sinus beats obtained from same MCG recording. MCG data of ten subjects studied using a 99-channel cardiomagnetometer (Elekta Neuromag Oy) over anterior chest were used. Data were averaged using atrial wave template and cross-correlation. Sinus beats with correlation less than 90% were considered to represent different morphology and averaged separately. Onset and offset of depolarization were determined automatically after 40 Hz high-pass filtering. Isofield integral maps were formed over the whole atrial wave, over the first and last 30 and 50 ms. Location, strength and direction of maximal gradients were determined from each integral maps. The velocity and movement of maximal gradient were followed also at 1 ms intervals. In 4 of 10 subjects a clear difference between the two morphologies was detected at the atrial wave onset while in 3 cases distinct separation were seen at the last portion of activation and in the other 3 cases in the middle of the atrial wave.

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On the Optimization of Spatial Filter to Construct Three-Dimensional Current Density Imaging from MCG Signal

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 3ICS Ltd., 4Shinko-Seisakusho Ltd., 5Tokyo Denki University, 6Iwate Medical University

We have developed the way to create current density imaging of bio-magnetic field, so far [1]. The three-dimensional (3D) imaging will become a powerful and promising tool for the diagnosis of the myocardial ischemia and infarction, if it would be available for the heart. To display 3D image for the heart contains a different problem from the case of brain. The heart activity should not be displayed by a set of a few dipoles unlike the brain, but rather by a widely spread current distribution. We are treating with this problem by using the spatial filter method made by modified Minimum Norm (MN) with Tikhonov regularization, which is based on the work by Pesola and Nenonon [2]. We have showed that our method represents realistic current density image [3]. However, the depth information obtained by this method is not accurate. It contains 2 cm error at 10cm beneath the sensors [1]. The next step is to find the optimization for Tikhonov parameter. In this study, we will show some attempts to extend NM algorithm for getting optimized spatial filter. The current density imaging for some MCG data will be shown.

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Generation of Cardiac Action Potentials with Multi-dipole Current Sources in Heart Phantom

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ABSTRACT

The cardiac conduction system coordinates the production and pathway of the cardiac action potentials that cause the heart to beat. Each region of the heart has cells with slightly different action potentials. We generated those potentials of eight types using look-up table and interpolation technique. The Waveform similar to ECG was obtained by adding all of cardiac action potentials. In adding, each action potential was properly weighted by values between -2 and +2. Adjusted potentials were injected in heart phantom with ten dipole current source using D/A converter system. The spatial distribution of magnetic field produced by multi-dipole current sources was evaluated with iso-field contour mapping and current arrow mapping. Utilizing the generation system of cardiac action potentials and the heart phantom developed in this study, we found that the physiological conditions of the heart could be tested. Our results provide quantitative data for the influence of changes in electric activation of the heart.

KEY WORDS: Conduction system, cardiac action potential, heart phantom, dipole

INTRODUCTION

Recently, the concern with the measurement of the magnetic field generated from heart and brain using SQUID sensor has been growing. Human body is often modeled as being piecewise homogeneous and isotropic in its electrical properties. However, in some tissue types the conductivity is strongly direction-dependent. Myocardium, brain and ordinary muscle tissue are examples of such an anisotropy. In the myocardium, as well as in ordinary muscles, which favors the electric conduction into the direction of the cells and hinders the conduction in the perpendicular directions [Karvonen, 2002].

In this article, we would like to explore the cardiac action potential and the heart phantom included multi-dipole. The measurement of magnetic field from phantom is related to the development and evaluation of the technique of source localization [Sosnytsky, 2002]. In addition, the phantom can be used as a standard magnetic source.

METHODS

Figure 1(a) shows the current dipole that is fabricated by twisted copper wire pair and round tube (diameter 5mm). The distance between two tip of 'T' shape is 10 mm. And a pair of the twisted copper wire was fixed in round tube as filled silicon. The non-magnetic material with the shape of sphere and adult heart was employed. An artificial current dipole was placed at two positions or ten positions in a spherical phantom and two heart phantoms. The phantom was first filled with a 0.9% saline solution. The phantoms with two or ten current dipoles are presented in Figure 1(b)-(d).

In this article, each current dipole was placed such as at the sinoatrial node, at the boundary between right and left atrial, at the atrioventricular node, at the bundle of HIS, at the left bundle branch, at the right bundle branch, at the left Purkinje fiber, at the right Purkinje fiber, at the endocardium of left ventricle, at the endocardium of right ventricular, and at the epicardium of ventricle.

The action potentials of the conduction node of heart were simulated during 700ms periods. Each action potential, 7000 samples interpolated by piecewise cubic Hermite function from 29 samples based on physiological characteristic of heart, appeared in Figure 2(a)-(h). We could properly compose of a wave that is quite similar to ECG wave with the weighted action potentials. Figure 3 shows the composition of ECG wave. And the GUI program for controlling current dipoles of phantom was developed. It is enable to control the heart rate and the gain of each cardiac action potential. The cardiac action potentials were generated in the notebook computer, and then digital waveforms were converted into analog waveforms with D/A converter (DAQcard-6715, NI corp., USA) in order to supply current to the phantom. Respective two current dipoles placed at the left and right bundle branch, Purkinje fiber, and endocardium were supplied with the same source. Therefore, eight cardiac action potentials were connected with ten current dipoles within the heart phantom.

The measurements of the magnetic field were performed with 61-channel DC SQUID system (Eagle Tech corp., Japan). The signals were band-pass filtered to 1Hz – 100Hz, digitized with the sampling rate of 500Hz. Firstly, Input nodes of the spherical and heart phantom with two current dipoles were connected with the function generator. Each current dipole was activated with a sinusoidal 20Hz or 30Hz current. Secondly, the heart phantom with ten current dipoles using current control system (notebook computer and D/A converter) for generating various cardiac action potentials was tested.

RESULTS

When activating each dipole with a sinusoidal 20Hz current in the spherical phantom, acquired magnetic field is presented in the top of Figure 4(a). Its contour map and current arrow map are shown in the middle and bottom of Figure 4(a), respectively. It was found from the result that the direction or position of each dipole and SQUID sensor was corresponded in the figure. Figure 4(b) shows the recorded magnetic field, contour map, and current arrow map at 88msec while 30Hz current is injected in the heart phantom. In this case, we only used the single dipole placed at the bundle of HIS. The results obtained were corresponded to our intention in current flow. When activating single dipole with ECG wave decomposed by using current control system and D/A card in the heart phantom, the results are shown in Figure 4(c). The measured magnetic field is very similar to real MCG signals. Also, its contour map and current arrow map showed the similar result in comparison with real MCG maps. But, we could obtain that measured magnetic fields indicated the shape of the first derivatives of a waveform composed with current control system. When activating ten dipoles with each action potential by using our system, the results are shown in Figure 4(d).

DISCUSSION

The design of phantoms, generation of cardiac action potential, and current control system has been described. Also, we have analyzed the magnetic fields that generated by the phantom and current control system. The sphere and heart phantom with two or ten dipoles were used in our experiment. The analysis of the contour map and current arrow map was performed. We could confirm that its results correspond to the orientation of dipoles in the phantom. For the experiment of heart phantom included ten dipoles we could find that there is a possibility of the generation of the

magnetic field similar to the real MCG signals. This result leaves room for various interpretations. But it seems reasonable to conclude that our phantoms and current control system included the program for the generation of cardiac action potential source can be used as a standard source for developing the SQUID system or an instrument for evaluating the characteristic of heart conduction system. A further direction of this study will be to provide more evidence for this result.

ACKNOWLEDGEMENTS: This work was supported by the grant from the Ministry of Commerce, Industry and Energy, Republic of Korea.

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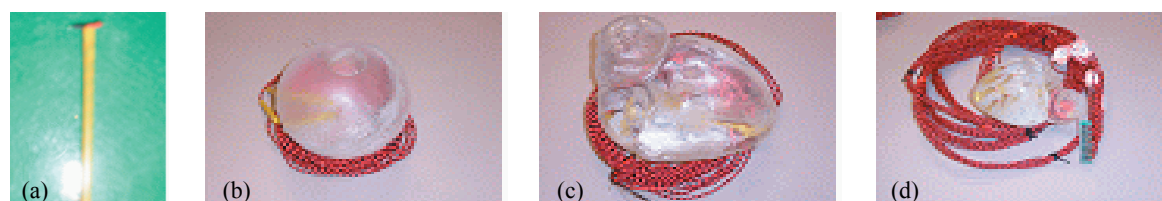


Figure 1. Phantoms (a) dipole structure (b) spherical phantom with two dipoles (c) heart phantom with two dipoles (d) heart phantom with ten dipoles.

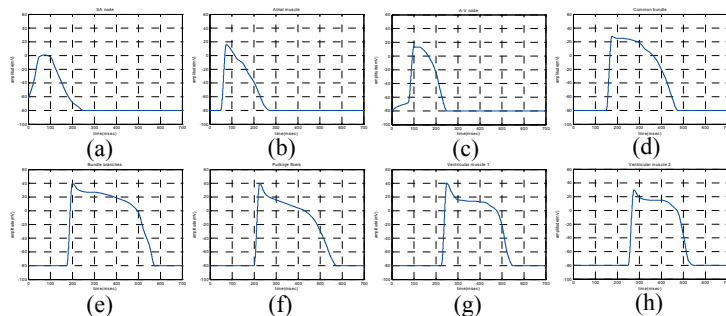


Figure 2. Cardiac action potentials of (a) SA node, (b) atrial muscle, (c) AV node, (d) bundle of HIS, (e) bundle branch, (f) Purkinje fiber, (g) endocardium of ventricle, and (h) epicardium of ventricle are generated by our system.

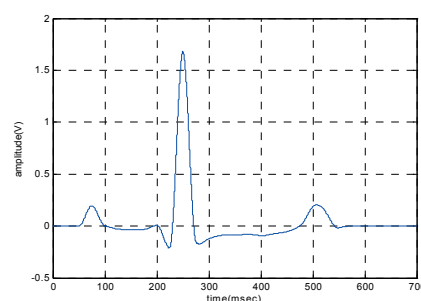


Figure 3. The composition of ECG wave.

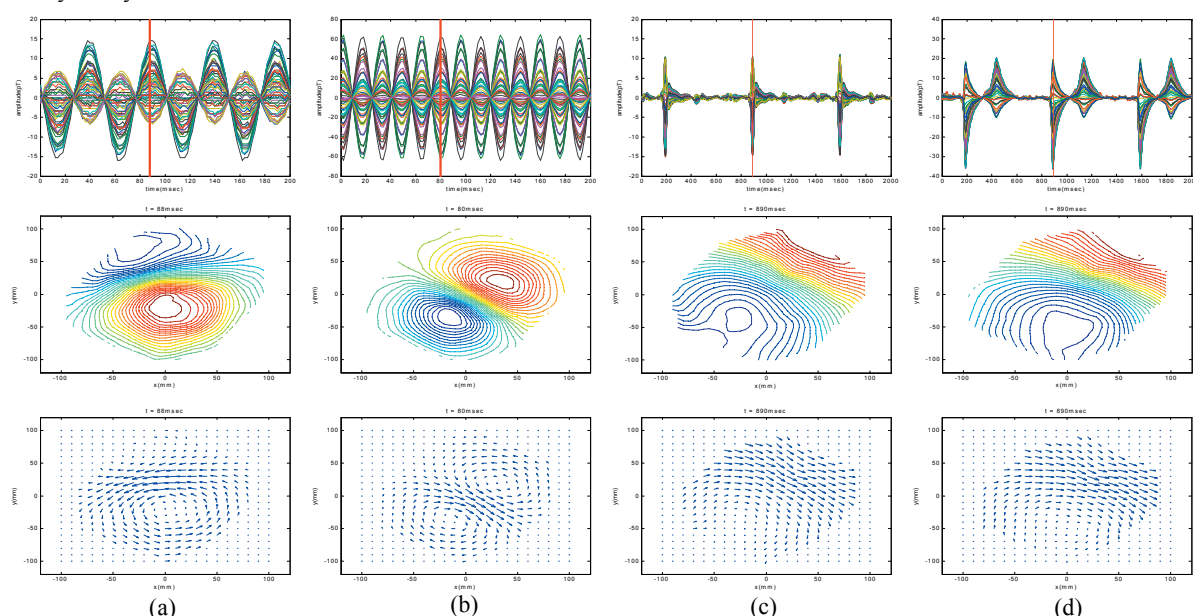


Figure 4. Measured magnetic fields, iso-field contour mapping and current arrow mapping in (a) spherical phantom and (b)-(d) heart phantom.

Spatial current dispersion pattern that characterize and separate the Brugada syndrome and complete right-bundle branch block

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ABSTRACT

The aim of this study was to detect patterns of spatial-current distribution in the late QRS and early ST segments that distinguish Brugada-syndrome cases from complete right-bundle branch blocks (CRBBBs). Magnetocardiograms (MCGs) were thus recorded from Brugada-syndrome patients, CRBBB patients, and the members of a control group. The current distributions were calculated as current-arrow maps (CAMs). We found an abnormal current from the RVOT to the left-upper chest in Brugada syndrome.

KEY WORDS

Brugada syndrome, Magnetocardiogram, Right-bundle branch blocks, current-arrow map

INTRODUCTION

We have developed a magnetocardiogram (MCG) system which provides us with maps of the current distribution in the heart; investigating the role of current distribution in the Brugada syndrome is a good application for this system. The plots of the tangential components of the magnetic field (or the tangential vectors calculated from the normal components of a magnetic field) show a visible pattern of peaks immediately above electrically activated regions [Hosaka 1976] [Tsukada 1998] [Tsukada 1999] [Horigome 1999]. The visualization technique has provided a high detection rate of abnormalities in the diagnosis of ischemic and arrhythmic heart diseases in adults [Tsukada 2000a] [Tsukada 2000b] [Yamada 2001] [Kandori 2001a] [Kandori 2001b] [Kandori 2002b] [Sato 2001] [Sato 2002] [Shiono 2002] [Kanzaki 2003]. In particular, MCGs of adults with long-QT syndrome (LQTS) were measured and current distributions were estimated with the aim of understanding the underlying mechanism [Kandori 2002b]. In the present paper, we introduce the detection of abnormal current in the patient with the Brugada syndrome [Kandori 2004].

METHODS

Magnetocardiograms (MCGs) were thus recorded from Brugada-syndrome patients (n=6), CRBBB patients (n=4), and the members of a control group (n=33). The current distributions at the six time points from Q onset were estimated by producing current-arrow maps (CAMs). The angle of the current arrow of maximum amplitude at each time point was calculated.

RESULTS

In the Brugada cases, the characteristic ST elevation was seen above the right-upper chest and abnormal currents (Fig. 1) appeared to be present in the right-ventricular outflow tract (RVOT). The angles of the abnormal arrows were $-78^{\circ} \pm 51^{\circ}$ at 100 and $-50^{\circ} \pm 61^{\circ}$ at 110 ms. In the cases of CRBBB, wide S and R waves were recorded above the right-upper and right-lower chest, respectively. The angles of the abnormal arrows for CRBBB were $152^{\circ} \pm 19^{\circ}$ at 100, $159^{\circ} \pm 20^{\circ}$ at 110, and $157^{\circ} \pm 19^{\circ}$ at 120 ms [Kandori 2004].

DISCUSSION

We consider that the pattern of MCG waveforms and abnormal current direction seen in the CAM provide critical signs that allow us to identify and distinguish between Brugada-syndrome and CRBBB patients. The direction may reflect the differences between action potential duration.

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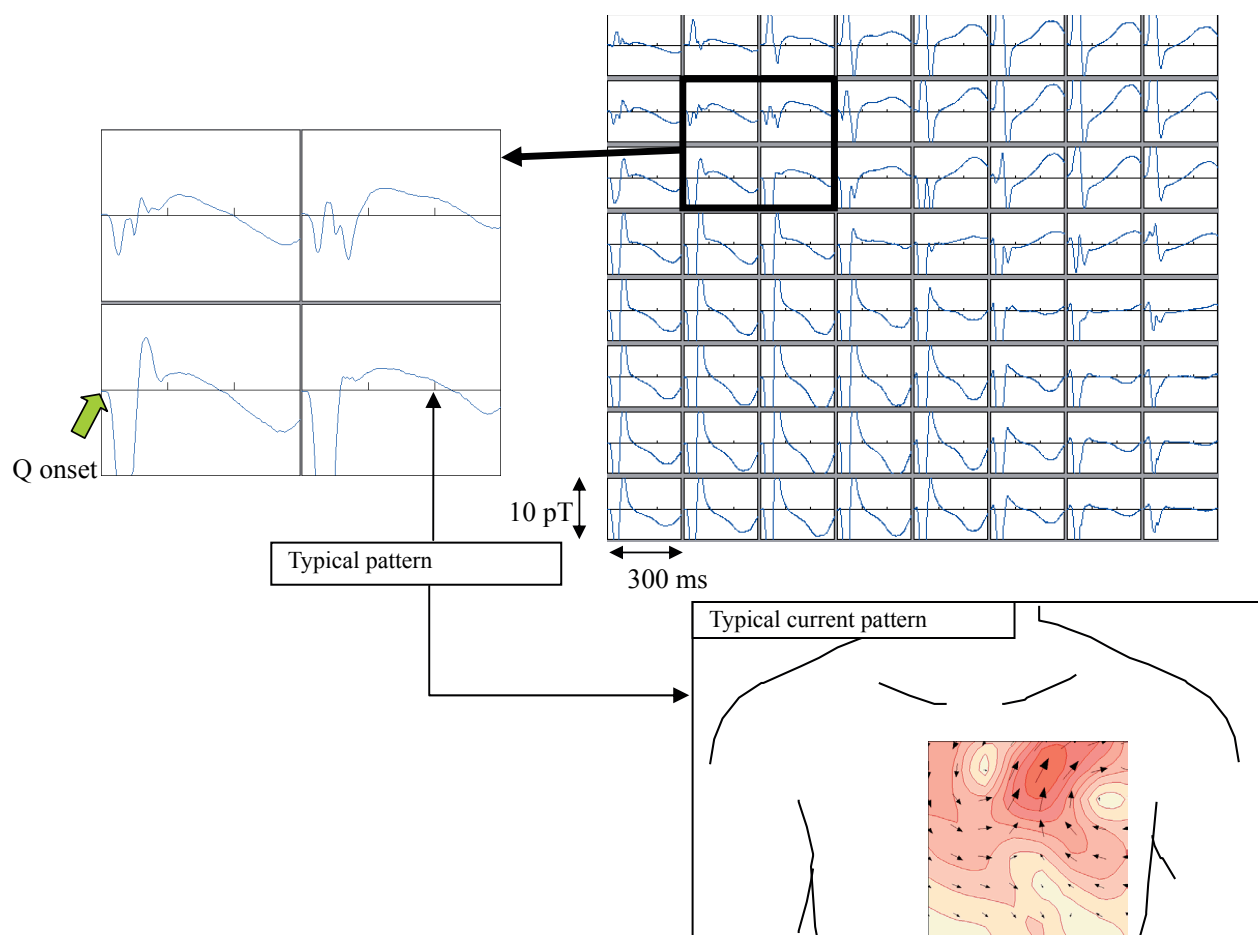


Fig. 1 MCG waveforms and current arrow map in patient with Brugada syndrome

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Averaging Algorithm Based on Data Statistics in Magnetocardiography

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ABSTRACT

An algorithm for automatic averaging of a magnetocardiogram (MCG) is described. Due to the relatively low signal to noise ratio in the MCG, the measured MCG data are often averaged to be analyzed. Generally, R-peaks are used as trigger points, which become anchors for superposition and we can obtain an averaged epoch eventually. However, we have to determine several parameters, such as the threshold magnitude for recognizing R-peak, the time-period of the epoch window, and which channel has dominant R-peaks. In order to determine these parameters automatically, we utilize the magnitude histogram of the root-mean-square waveform of all the channels. We can determine the threshold magnitudes for recognizing R-peaks and T-peaks, respectively, by using the characteristic distribution of the MCG signal histogram. Peak detection procedure using these thresholds records all the locations of the R-peaks and T-peaks, thus we get the average latencies of the R-T intervals and the R-R intervals. From these latencies, we estimate the full width of the epoch window. By adding a routine for processing double R-peaks, our algorithm could conduct the MCG averaging sequence full-automatically. The algorithm has been tested on recordings of 40 normal subjects and 15 patients suffering from myocardial ischemia, and we conclude that this algorithm reliably performs the averaging sequence. The MCG recordings are measured by our 62-channel planar gradiometer system in a magnetically shielded room.

KEY WORDS

Magnetocardiography, peak detection, statistical thresholding.

INTRODUCTION

The first task of MCG analysis in time domain or even in finding current sources is to get an averaged heartbeat waveform because of relatively low signal to noise ratio (SNR) in an MCG. Averaging N heartbeats will improve the SNR by a factor of $\sqrt{N}$. In order to average the measured heartbeats, we have to decide triggering points in the time series. Generally, R-peaks are used as the triggering anchors for superposition. For the R-peak detection, we may use various algorithms those have been developed for QRS detection in electrocardiography (ECG). Some representative methods are using differential filters, least absolute deviations (LAD), normalized cross correlation functions (NCCF) [Jain, 1981], and morphological inflection angle detection [Hsiung, 1989]. Although there are automatic gain control feedback loops that change threshold values by the slopes of the QRS complex already detected, the differential filter method still requires the first visual QRS notification. The LAD and NCCF also need a priori the reference template of a QRS complex. In case of the morphological inflection angle detection, it takes relevantly long time to conduct the process of the QRS detection.

In this study, we propose a full-automatic averaging algorithm for a multi-channel MCG system. Especially, this algorithm is used for a pre-processing before solving an inverse problem to obtain a myocardial current source distribution. The algorithm adopts a simple over-threshold peak detection method. For the full-automatic operation, we have to decide several parameters, such as the threshold level, the epoch length corresponding to one heart cycle, and selection of the R-peak-dominant channel. In comparison of MCG with ECG, the amplitude of MCG signal is rather variable and it is difficult to fix the threshold level. Moreover, the representative waveforms of MCG are not constructed yet because there is no standard MCG sensor type and no standard measuring positions, which makes us embarrassed to select the triggering channel. We should also consider the proper length of the epoch window for averaging. If the window width is not enough to cover one heartbeat, the averaged waveform will get truncated and we will lose information. On the contrary, if the window width is excessively wide, some extra features from the foregoing beat or the following beat will be superposed. To circumvent these problems, we decide the threshold level and the epoch length by using the characteristic statistical distribution of the MCG signal.

We describe the detailed methods for the statistical threshold decision in the following section. We test this algorithm by applying it to MCG recordings measured by our 62-channel MCG system [Lee, 2004].

METHODS

At the first process, we reject the baseline wandering in a measured MCG. The breathing of a subject or environmental changes, such as car movements, results in a different baseline drift at each channel. We utilize a morphological filtering technique [Mun, 2004] to compensate the changed baselines because the technique is fast and effective in reserving the R and T peaks, which are the handling objects in our algorithm.

The second step, we make the root-mean-square (RMS) waveform of all the channels. By doing this, we do not have to select a R-peak dominant channel because the position of the largest peak in the RMS waveform implies the instant of maximum depolarization of heart muscle, which reflects cardiac excitation information from all the channel. Figure 1 shows the RMS waveform of MCG. Now, we should decide an appropriate threshold level for R-peak detection. As you can see in Fig. 1, T-peaks in the RMS waveform have a tendency to grow up to the comparable level of R-peaks. Therefore, we have to make the threshold level positioned between the R-peak level and the T-peak level. To do this, we produce the histogram of magnitude of the whole length of the RMS waveform (Fig.2). In the histogram, we can see the characteristic magnitude distribution due to the regular shape of MCG signals, i.e. small peaks at the level knees in the histogram. From the right to the left, the small peaks correspond to the R-peak

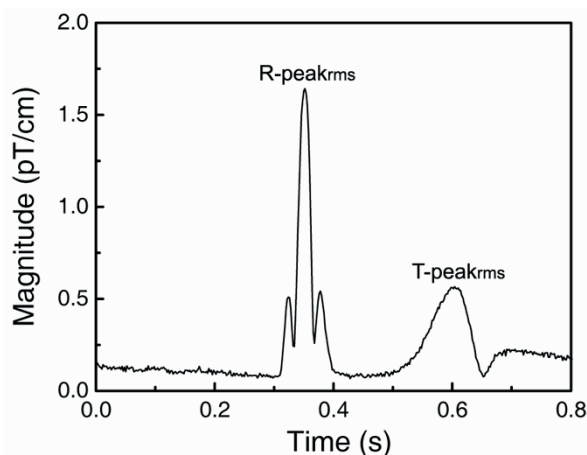


Figure 1. The RMS waveform of MCG.

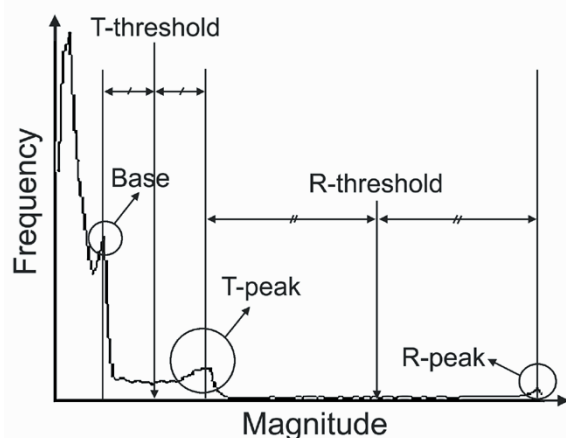


Figure 2. The histogram of the magnitude of the RMS MCG. Note the peaks at the knees. These peaks correspond to the characteristic peaks in the MCG time-series.

RESULTS

We collected MCG data by using our 62-channel SQUID gradiometer system in a magnetically shielded room [Lee, 2004]. The system that measures the tangential component of magnetic fields [Kim, 2004] has been installed at Cardiovascular Center in Yonsei University Medical Center. In order to validate the performance of our algorithm, we applied the algorithm to the recordings of 40 normal subjects and 15 patients suffering from myocardial ischemia. All the recordings were measured two times for each subject with different sampling rates (500 Hz and 1500 Hz). 60-Hz line notch filtering and 0.1 Hz high pass filtering were applied before 16-bit resolution data acquisition. Our algorithm has worked successfully with all the recordings except just one case. The failure was due to abnormal electrical systematic noise, i.e. noise from an instantly misgrounded circuit.

DISCUSSION

In order to perform MCG analysis, it is important to make a simple operation for an averaging process because averaging is a kind of basis processing. The automatic parameter decision using statistical MCG signal characteristics, which was proposed in this study, made the averaging process completed with a one-click operation. Our MCG analysis software, KRISSMCG, has been equipped with this algorithm for noise reduction and has been making a pre-diagnosis on the case of myocardial diseases in hospital. Originally, this algorithm was developed for noise reduction in the S-T interval having information on myocardial ischemia. The MCG of severe ventricular tachycardia, such as ventricular fibrillation, will not show the well-defined R-peaks, and applying our algorithm to the case will give a failure. However, the MCG of such case does not require any averaging process to be analyzed so it is beyond the subject.

ACKNOWLEDGEMENTS

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magnitude, the T-peak magnitude, and the other base level, respectively. Thus, we can estimate the magnitudes of R- and T-peaks by detecting the peaks in the histogram. The peak detection algorithm fits a quadratic polynomial to sequential groups of data points and a specific number of data points are used in the fit. We decide the median value between the R-peak magnitude and the T-peak magnitude as the threshold value, and mark the R-peak positions by using the same peak detection algorithm with the decided threshold level. When multiple R-peaks appear in short duration, we consider the first R-peak to be the triggering anchor.

The third step, we determine the length of the epoch window to be superposed. It can be naturally assumed that the length of a heartbeat is proportional to the latency of an inter-beats structure, and we obtain the latency between the R-peak and the T-peak. We already know the positions of R-peaks and we can eliminate the R-peaks from the RMS waveform. Then, we decide the median value between the T-peak and the base level as a T-threshold value, and mark the T-peak positions with the threshold level. The averaged length of the R-T interval can be acquired. The epoch window is defined as from the instant of 1.2 times the R-T interval before the R-peak to the instant of 1.4 times the R-T interval after the R-peak (Fig. 3). When the measured MCG has irregular T-peak patterns, the number of the detected T points is different to the number of the detected R points. In that case, we substitute the 1/3 of R-R interval for the R-T interval. We cut the epoch windows at every R-peak and superpose them to make an averaged waveform for every channel.

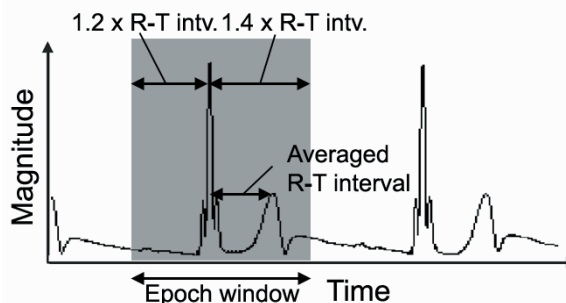


Figure 3. Decision of the width of the epoch window to be superposed. The width is proportional to the mean R-T interval.

Optimal Sensor Distribution for Measuring the Tangential Field Components in MCG

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ABSTRACT

We discuss the optimal arrangement of detectors for our 52-channel magnetocardiogram (MCG) system measuring tangential components of the cardiac magnetic fields. Nowadays, most MCG instruments are designed to cover the whole heart area so that all information available from the myocardial magnetic field can be simultaneously measured. In such a system, detectors should be spread over a sufficiently wide area and the diameter of the cooling dewar increases. The larger the size of the dewar the more heat-loss occurs and the higher the cost of production. The consumption of refrigerants is connected directly with the cost of maintenance. Therefore, we reviewed the spatial sampling theory to determine the proper interval between detectors, and we decided on the number of channels to cover the whole heart area. In order to fit the detector array on the cylindrical dewar economically, we removed the detectors that had been located at the corners of the array square. Through simulations using the confidence region method, we verified that our design of the detector array is enough to obtain whole information from the heart at a time. A result of the simulation also suggests that tangential-component MCG measurement can localize deeper current dipoles better than normal-component MCG measurement with the same confidence volume; therefore, we would conclude that measurement of the tangential component is more suitable to an MCG system than measurement of the normal component.

KEY WORDS:

Magnetocardiogram, spatial sampling theory, confidence region.

INTRODUCTION

Nowadays, full-size multichannel MCG systems, which cover the whole signal area of a heart, are developed to improve the clinical analysis with accuracy and to provide patients with comfort in the course of measurement. To design the full-size MCG system, we have to make a compromise between cost and performance. The cost is involved with the number of sensors, the number of the electronics, the size of a cooling dewar, the consumption of refrigerants for maintenance, and etc. The performance is the capability of covering the whole heart volume at once and of localizing current sources with a small error. In this study, we design the cost-effective arrangement of sensors for MCG by considering an adequate sensor interval and the confidence region of a tolerable localization error, which covers the heart.

SENSOR INTERVAL

We can apply the spatial Nyquist sampling theorem to decide the interval between adjacent sensors of an MCG system [Ahonen, 1993]. Our sensor measures the tangential component of biomagnetic fields. Let us consider the spatial spectrum of the tangential magnetic field component, B_x , at the height of z , when current, J_y , flows on the x - y plane. If we use the convolution theorem, the Fourier transform of B_x can be written by,

$$b_x(k_x, k_y, z) = g_x(k_x, k_y, z) j_y(k_x, k_y) = \mu(dz) \frac{e^{-kz}}{z} j_y,$$

where g_x is the Fourier transform of the Green function obtained from the Biot-Savart law, μ is the magnetic permeability, dz is the thickness of the source current plane, and $k = \sqrt{k_x^2 + k_y^2}$. The equation effectively shows low-pass filtering characteristics. Especially for a high sensor position, i.e. a large z , the spatially high frequency component of the measured magnetic field decreases exponentially. Numerically, the 99% of the spatial spectral power is confined below the spatial frequency of $1/2z$. In the Nyquist theorem, the existing maximum frequency should be $1/2d$ to prevent aliasing when the sampling interval is d , and hence $d \leq z$.

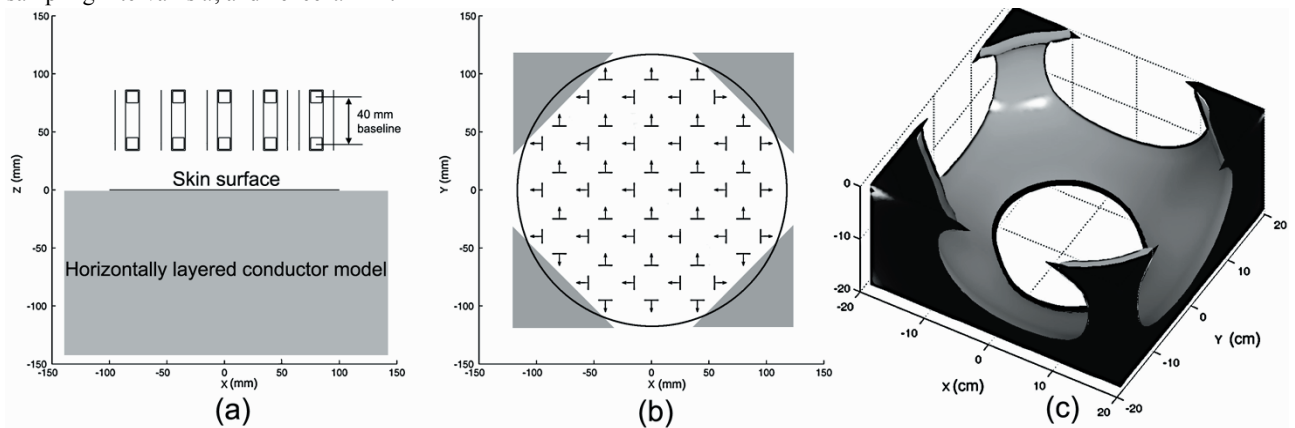


Figure 1. Sensor arrangement of the 52-ch. MCG system in the x - z plane (a) and in the x - y plane (b). The arrows indicate the directions of pickup coils. The hollow of the figure (c) represents the confidence region of the tangential sensor array.

In MCG measurement, a heart is located about 3 cm below the surface of the thorax and the dewar has a gap more than 1 cm for thermal insulation. Therefore, the minimum z would be more than 4 cm. Consequently, the sensor interval less than 4 cm can acquire sufficient information at the height of the sensor array without aliasing.

THE AREA OF SENSOR ARRAY

Once the proper sensor interval is decided, we should decide the sufficient area of the sensor array to localize the source current on the heart muscle. The general size of a normal heart is about 13 cm in length, 9 cm in width, and 6 cm in anteroposterior. However, we cannot know the exact position of a patient's heart because of individual differences. Therefore, we need to consider some extra margin in the detectable area. In order to estimate the detectable area, we calculated the confidence region that was defined as the spatial range having the localization error less than 1 cm^3 with 95% probability [Sarvas, 1987]. The distribution of the localization error was approximated by confidence ellipsoids, which was computed by SVD [Fuchs, 2004]. The arrangement of sensors and the conductor model that was used in the computation are depicted in Fig. 1. The sensor array consists of pairs of x- and y-direction planar gradiometers with a 4-cm baseline (Fig. 1a). The FRP LHe dewar has a cylindrical shape. If we pack a square sensor array into the cylindrical dewar, so much extra space remains. This is not desirable because the vaporization ratio of LHe is proportional to the diameter of the dewar and the long-diameter dewar will hit the chin of a patient. Therefore, we removed sensors in the gray corner of Fig. 1b. When the interval is 40 mm, the number of the sensors is 52 and we can use a dewar of 20-cm inner diameter. The jar-shaped hollow in the Fig. 1c represents the confidence region of the sensor array. Here, we assumed a horizontally layered conductor model with the skin surface at $z=0$, a random gaussian sensor noise of $20 \text{ fT}_{\text{rms}}$, and the current source moment of $1 \text{ } \mu\text{A} \cdot \text{m}$ with (1,1,0)-direction. Usually, the errors in the longitudinal direction, i.e. parallel to the direction of source current moment, are larger than in the transversal direction. If we consider the longitudinal direction for rigorousness, the diameter of the confidence region at the 10-cm depth is about 38 cm, which is enough to cover the heart volume.

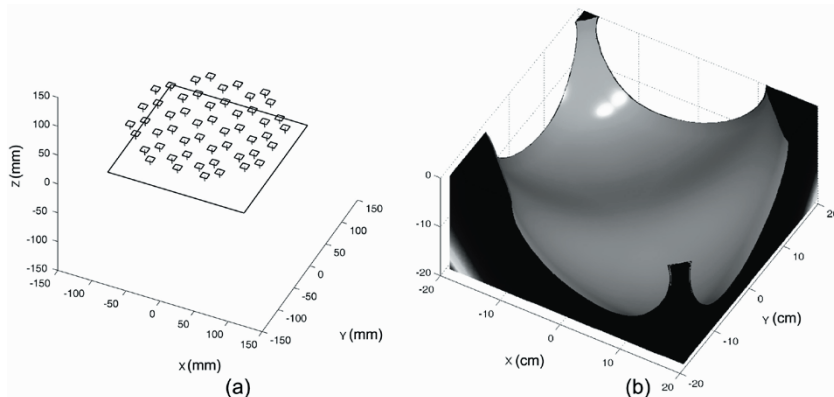


Figure 2. (a) Sensor arrangement of a normal-component-measuring MCG system. (b) The hollow represents the confidence region of the normal sensor array.

COMPARISON WITH THE NORMAL COMPONENT MEASUREMENT

For the comparison between the tangential-component-measuring sensor system and the normal-component-measuring system, we computed the confidence region of the sensor array that has the same sensor positions with the previous case but measures the magnetic field components of the normal direction (Fig. 2). The bowl-shaped confidence region appears. For the more detailed comparison, we show the diameter of the confidence region as a function of the current source depth in Fig. 3. Considering the longitudinal direction, we can see that the normal sensor array has a narrower confidence region than tangential sensor array at below 3-cm depth. For a current dipole at the depth of 15 cm, the normal sensor array has the confidence region diameter less than 13 cm (the heart length), while the tangential sensor array has the confidence region diameter of about 32 cm. For the sources located below 17 cm, the normal sensor array cannot localize the dipole with a tolerable error. Therefore, we can conclude that the tangential-component-measuring system would be more suitable to construct the full-size multichannel MCG system because the tangential sensor system can localize a deeper source with a smaller area of the sensor array in comparison with the normal sensor system.

DISCUSSION

In this study, we designed an efficient sensor array for a full-size MCG system with tangential-component-measuring SQUID sensors. In practice, some sensors can be dead and an additional environmental noise will contract the confidence region. Therefore, we had better make some margin in the sensor array optimization, i.e. a smaller sensor interval and a wider array area. As a conclusion, we insisted that the tangential sensor system is better than the normal sensor system to fabricate an MCG system. However, the authenticity of this argument could depend on the employed conductor model. As a future work, we should test the argument for a realistic heart model, such as an MRI-segmented boundary element model.

ACKNOWLEDGEMENTS:

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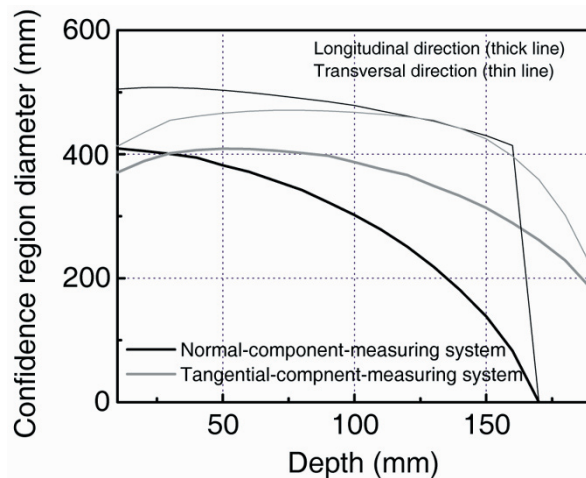


Figure 3. Confidence region diameter as a function of the current source depth for the normal and tangential sensor array.

Neonatal magnetocardiography

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ABSTRACT

The aim of the present study was to test the validity of magnetocardiography (MCG) in the estimation of neonatal cardiac rhythm. Our study population consisted of 51 neonates who were delivered normally between 37-41 weeks of gestation from clinically uncomplicated pregnancies. There was also a neonate included in the study in which the diagnosis of "hypoplastic left heart syndrome" was demonstrated by U/S Doppler examination. Maternal age ranged from 18 to 39 years (mean=29.15, SD=6.13). Our study results revealed 44 neonates with normal cardiac rhythm, four with ventricular tachycardia (VT), one with ventricular tachycardia (VT) and extrasystolic beats and one with bradycardia. The neonate with the hypoplastic left heart syndrome presented frequent episodes of ventricular bigeminy in the magnetocardiographic trace. M-mode echocardiography confirmed the diagnosis of the seven cases of arrhythmia in our study group. The neonates who presented pathologic cardiac rhythms were under close cardiologic examination with M-mode echocardiography for a period of two months. The arrhythmia disappeared 7-10 days after delivery. M-mode echocardiographic recordings of the cardiac motion with time were obtained using a single M-mode sampling line. A number of studies reported in the past refer to certain advantages, which MCG offers compared to M-mode echocardiography, two dimensional imaging, pulsed Doppler and colour flow Doppler. Results gained from the study lead us to believe that MCG could provide clinical practice with a non-invasive, rapid and easy to perform method, which could be used as an adjunct to conventional methods for the evaluation of neonatal cardiac rhythm.

KEY WORDS:

Magnetocardiography, neonate, arrhythmia, normal cardiac rhythm

INTRODUCTION

Magnetocardiography is a promising, completely noninvasive method to obtain functional information about electrical activation in the human heart. The electrophysiological activity is associated with a magnetic field detectable without contact to the body surface. In 1986, Roth and Wikswo presented calculations of a theoretical example of electrically silent magnetic fields. They showed that for tissues with an assumed complex conductivity, some information was lost in the electric potential, but was detectable with a biomagnetic sensor. Van Oosteron and co-workers [1990] concluded from measurements and simulations of MCG and ECG that, for the ventricular depolarization, the contribution of electrically silent magnetic fields is only marginal. In contrast MacAuley et al. [1985] suggested that MCG signals of the QRS offer information that is not available with the ECG. Although MCG has been known for almost 30 years, its clinical use have been limited to localize myocardial conditions as Wolff-Parkinson-White (WPW) syndrome, ventricular tachycardia (VT) and myocardial ischaemia in adults. The magnetocardiographic investigation of patients with WPW syndrome, ventricular extrasystoles, VT and paced ventricular arrhythmias demonstrated that MCG permits a non-invasive localization of arrhythmogenic tissue with high spatial accuracy. To our knowledge there are no reports in the literature concerning the efficacy of MCG in the estimation of neonatal cardiac rhythm, thus the goal of this study was to investigate the validity of MCG in the estimation of neonatal normal and pathological heart rate.

METHODS

Our study population consisted of 54 neonates who were delivered normally between 37-41 weeks of gestation from clinically uncomplicated pregnancies. Maternal age ranged from 18 to 39 years (mean=29.15, SD=6.13). In 3 of the 54 neonates it was not possible to measure the MCG signals due to technical reasons. The MCG was recorded digitally for 10 min by a single channel biomagnetometer (DC-SQUID model 601, USA). We digitized the signals using 12-bit precision analog to digital converter with a sampling frequency of 256 Hz. The MCG signals were band-pass filtered with cut-off frequencies of 0.1-100 Hz. The associated Nyquist frequency limit with the above-mentioned sampling frequency is 128 Hz, which is well above the constituent frequency components of interest in MCG recordings and avoids artifacts. The tip of the single channel biomagnetometer was placed 2-3cm above the infants' heart at the position where the QRS signal was found to be at its maximum. The rules of the Helsinki Declaration were followed: parents were fully informed and a written consent was obtained for each newborn. The local ethics committee was notified and approved of this study. Throughout the entire period of measurement, a sleep state analysis was carried out, focusing on quiet sleep. Closed eyes, absence of body and eye movements and a prevailing muscle tone defined quiet sleep states. Biomagnetic recordings were obtained in the 2nd day after birth to avoid the influence of the pharmacological treatment of the pregnant women during gestation. All infants breathed spontaneously during the measurements. The measurements began at 11:00 am~1 h after the last feeding. The biomagnetometer allows on-line determination of the R-R intervals. After the R-R interval is determined, the segment of the digitally recorded MCG signal is compressed and stored together with the R-R interval for later off-line analysis. The individual R-R intervals that deviated from the time series mean by >60% were removed and the segments from the beginning or end of the tracing where nonstationarity was existence, were cutting out. These criteria were chosen so that the respiratory rate of the free breathing infants would be as regular as possible.

RESULTS

Our study results revealed 44 neonates with normal cardiac rhythm, 4 with VT, 1 with VT and extrasystolic beats and 1 with bradycardia. The neonate with the hypoplastic left heart syndrome presented frequent episodes of ventricular bigeminy in the magnetocardiographic trace. M-mode echocardiography confirmed the diagnosis of the 7 cases of arrhythmia in our study group. The neonates who presented pathologic cardiac rhythm were under close cardiologic examination with M-mode echocardiography for a period of 2 months. The arrhythmia disappeared 7-10 days after delivery whereas the neonate with the hypoplastic left heart syndrome died at his 10th day of life. M-mode echocardiographic recordings of the cardiac motion with time where obtained using a single M-mode sampling line. Figure 1 presents a recording obtained from a newborn, with normal heart rate (120 /min). Figure 2 shows the magnetic recordings from a neonate with VT (180/min), whereas figure 3 presents a magnetocardiogram

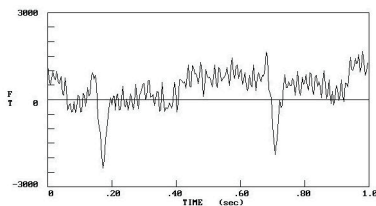


Fig.1. A normal neonatal MCG recording. Ventricular rate: 120/min (2 QRS complexes per sec).

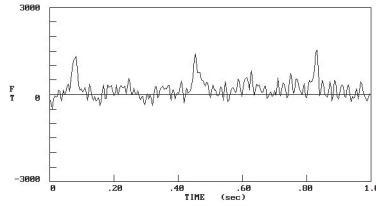


Fig.2. MCG recording presenting neonatal VT. Ventricular rate : 180/min (3 QRS complexes per sec).

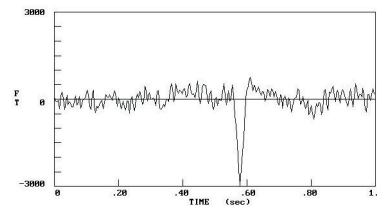


Fig.4. MCG recording presenting neonatal bradycardia. In one-sec period there is only one QRS complex (60/min).

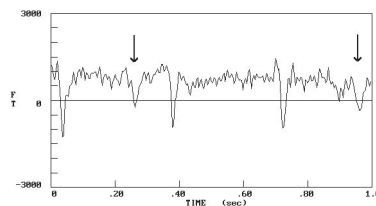


Fig.3. A neonatal MCG recording presenting VT with extrasystoles. The arrows show the extrasystoles. (180/min).

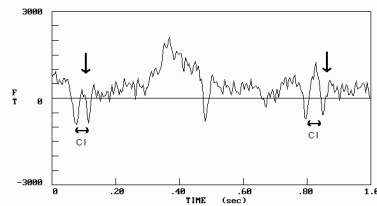


Fig.5. MCG recording presenting episodes of ventricular bigeminy in the neonate with the hypoplastic left heart syndrome. Stable couple interval (CI) for the same rate.

with VT and extrasystolic beats (180/min). Figure 4 shows the magnetic recordings from the neonate with bradycardia, where in 1sec duration interval there is only one QRS complex (60/min). The neonate with the hypoplastic left heart syndrome presented frequent episodes of ventricular bigeminy in the magnetocardiographic trace (Figure 5).

DISCUSSION

A number of studies reported in the past refer to certain advantages which MCG presents compared to other diagnostic techniques such as M-mode echocardiography, two dimensional imaging, pulsed Doppler and color flow Doppler [Wakai et al., 1997; Fenici and Melillo, 1993]. All the above-mentioned studies confirm the diagnostic accuracy of MCG, especially regarding functional heart disorders like cardiac arrhythmias. Fenici et al [1986] was the first who reported successful MCG localization of a sustained VT. Several authors have demonstrated that MCG is useful for the investigation of clinical arrhythmias, non-invasively, and for the identification of patients at risk for sudden death through the detection of magnetic fields. The detection of serious arrhythmias is of a great importance and especially in the patients at risk for sudden death. Thus any new non-invasive method, reliable, with predictive accuracy has potential importance. MCG provides a method of investigating normal and abnormal cardiac rhythm with high temporal and spatial resolution, applicable in the last decade. Its accuracy and reliability has been established with electrophysiology and cardiac pacing. Fujino et al [1984] have reported a higher sensitivity of the MCG as compared to the ECG in the detection of left ventricular hypertrophy. Makijarvi et al [1993] concluded that MCG mapping provides accurate localization of overt atrioventricular accessory pathways and some atrial arrhythmias, as focal atrial tachycardia can probably be localized by MCG mapping. Though our results cannot be compared to any others reported, we believe that MCG helps a lot in the detection of neonates whose cardiovascular system should be submitted to closer investigation. In conclusion we believe that MCG could provide a non-invasive, rapid and easy to perform method, for detecting neonatal arrhythmias. Of course, more studies in large series of infants and further technological innovation of the equipment used need to be done, before the method is established as a screening procedure in clinical practice.

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Magnetocardiographic image of the athlete's heart

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ABSTRACT

Aim of this study was to detect whether the magnetocardiography (MCG) could demonstrate new and characteristic features of the athlete's heart.

METHOD: Twenty endurance athletes (3 females and 17 males) were examined. Ten healthy controls were similarly tested. Next to the medical history and a physical examination all underwent a 12-lead ECG recording, most a 2 dimensional ECHO and all the MCG. From each individual approximately 20 current density vectors (CDV) maps were assessed at 10 msec. intervals during the entire ST-T period. The main principle of map classification was the existence or absence of dipole structure. Dipole maps were further specified based on their symmetry, equality of poles or current vortexes on the hypothesis that a stronger current vortex represents a zone of hyperconductivity , which is a characteristic features of the athlete's heart. The final MCG classification was therefore as follows: Group 1a – normal, “not well-trained”; Group 1b – normal, “well-trained”; Group 2 – “pathological”

Results: Five of the 30 examinations fell into group 2, one of these had a history of heart disease, later confirmed by independent tests. The other 4 had no history of heart disease. However, further examination showed significant abnormalities in the ECG and ECHO of two of these four persons. Of the remaining 25 persons, 23 were correctly classified as group 1a or 1b in accordance with their sportive history.

Conclusion: The presence of asymmetric current vortexes in the MCG maps during the ST-T period appears to be a characteristic parameter of the “athlete's heart”.

KEY WORDS

Magnetocardiography, sport medicine , mapping , athlete's heart

INTRODUCTION

In a recent study Pelliccia et al. analysed the 12-lead electrocardiographic (ECG) patterns in 1005 consecutive athletes participating in 38 sporting disciplines and compared these to echocardiograms (ECHO) [Pelliccia,2000] . Sixty percent of these athletes were found to have a normal ECG and ECHO but in 40% a variety of abnormal ECG patterns was seen, interpreted as indicative of physiologic cardiac remodelling. This was most striking in endurance athletes, such as cyclists, cross country skiers, long distance rowers, tennis and basketball players . These authors point out that in a small but significant group of these top athletes significant ECG abnormalities were found suggesting cardiovascular disease such as infarction or myocarditis while their ECHOs were normal. Although these changes were likely to reflect the (hopefully innocent) consequence of their long term, intense athletic training (and therefore a component of the athlete's heart syndrome), they do also represent a potential limitation to the predictive value of the routine ECG as part of (pre-)training evaluation.

The recent development of the Magnetocardiography (MCG) technique, described in previous chapters, has made it possible to record the MCG of healthy individuals and athletes outside the hospital setting, without the requirement of an examination room specially shielded against extraneous magnetic fields. It appeared of interest to compare the 12-lead ECG with the MCG in a group of normals and in a number of topathletes, to see whether the MCG might provide information beyond that obtained from the standard electrocardiogram, with the ECHO examination acting as a sort of reference.

METHODS

Twenty endurance athletes (3 females and 17 males), among whom 12 were marathon runners, 5 triathletes, 2 world class swimmers and 1 long distance cyclist (10 were < 37 years and 10 > 50 years) were examined by a Sports Physician. Ten healthy controls between 37 and 50 were similarly tested.

Next to the medical history and a physical examination all underwent a 12-lead ECG recording, most a 2 dimensional ECHO and all the MCG. The Magnetocardiograph was mounted inside a trailer, placed in front of the Sports Medicine Department of the Utrecht Medical Center, the Netherlands. An illustration of this arrangement is shown in chapter 2. The analysis of each test was done by an expert in that technique unaware of the results of the other test procedures.

From each individual approximately 20 MCG maps were assessed at 10 msec. intervals during the entire ST-T period. The main principle of map classification was the existence or absence of dipole structure. Maps with dipole structures reflect normal distribution of currents, in contrast, maps with non-dipole structure reflect pathologic distribution. Dipole maps were further specified based on their symmetry, equality of poles or current vortexes on the hypothesis that a stronger current vortex represents a zone of hyperconductivity.

They were classified into Group 1 “Normal” when 25% or fewer of these maps had a non-dipole structure. A further division was made into “well-trained” (more than 50% of these maps showed an obvious non-equal dipole) or “not well-trained” (fewer than 50% of the maps showed an obvious non-equal dipole). When more than 25% of the current density maps had a non-dipole structure, the patient was assigned to Group 2, “pathological”. The final MCG classification was therefore as follows:

Group 1a – normal, “not well-trained”

Group 1b – normal, “well-trained”

Group 2 – “pathological”

This “simplistic” MCG classification was compared to other tests classified in the usual manner.

RESULTS

Five of the 30 examinations fell into group 2, one of these had a history of heart disease, later confirmed by independent tests. The other 4 had no history of heart disease. However, further examination showed significant abnormalities in the ECG and ECHO in 2 of them. On the other hand, 2 others had a normal ECG, stress ECG and ECHO, in these the MCG should be considered as false positive.

Of the remaining 25 persons, 23 were correctly classified as group 1a or 1b in accordance with their sportive history. Of the last 2, one athlete was wrongly classified as group 1a and one non-athletic person was incorrectly classified as group 1b.

Thus two individuals showed an abnormal MCG, one was untrained, while the other was a reasonably well trained marathon runner. The clinically healthy persons with a borderline ECG showed either a group 1a or 1b MCG result.

DISCUSSION

Already as early as 1929, Hoogerwerf tried to use the electrocardiogram (ECG) as a tool to screen athletes for diseases, to detect pathological or physiological effects of intensive training and to measure the effect of training. He analysed 260 ECGs of topathletes during the Olympic Games in Amsterdam in 1928. However, it took up to 1967 before larger series of ECGs (up to 12,000) were recorded in athletes of many disciplines [Venerando,1979]. Reports on ECG findings in elite or subtop athletes of particular disciplines were also regularly published but almost never in large series. Among the few exceptions, Mosterd et al. published in 1987 the analysis of the ECGs of almost 1,000 Dutch top swimmers [Mosterd,1987].

Several authors addressed specific findings in the ECGs of athletes [Oakley,1982, Maron,1996] and stated that in particular the correct interpretation of T wave changes and repolarization disturbances was controversial and difficult. More sophisticated cardiological techniques such as exercise testing, echocardiography or nuclear imaging have subsequently been advocated [Corrado,1998].

Compared to the standard 12-lead ECG, the increased sensitivity and specificity of the MCG above other non-invasive techniques as demonstrated in previous chapters in this book, was confirmed in this small pilot study in athletes and healthy controls, with 5 of the 30 examinations showing a grossly abnormal MCG in the presence of a non-diagnostic or normal ECG. Among these 5, one apparently healthy individual was subsequently shown to have coronary artery disease by coronary angiography, of the remaining four, 2 had an abnormal MCG in the presence of an abnormal echocardiogram.

To conclude: the presence of asymmetric current vortexes in the MCG maps during the ST-T period appears to be a characteristic parameter of the "athlete's heart". Given the non-diagnostic information from the ECG in individual cases and the normal or inconclusive appearance of the Echocardiograms, the analysis of MCG maps could become useful to differentiate between highly trained athletes with striking ECG abnormalities but without cardiac morphological alterations and individuals with similar abnormalities in the presence of a myocardial disorder.

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Bayesian Classification of Myocardial Excitation Abnormality Using Magnetocardiogram Maps for Mass Screening

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ABSTRACT

We propose a novel classification method based on the Bayes rule to utilize the magnetocardiogram (MCG) in noninvasive mass screening. The cardiac excitation is directly tracked by the MCG field maps that provide the transition of the magnetic field generated by myocardial excitation current through the excited wave front. To adopt the characteristics of the excited wave fronts as a parameter for the Bayes theorem, we newly developed a parameterization procedure that consists of a two-dimensional wavelet approximation and a cluster analysis of magnetic field maps. With the parameter determined by this procedure, the probability of a subject to belong to objective disease or normal group is estimated by the Bayes theorem. The subject is classified into the group of the highest probability. We applied the proposed method to ST-T period of MCG data of 6 old myocardial infarction (OMI) patients and 15 normal controls. The method showed sensitivity of 83%; specificity, 100%; positive predictive value, 100%; and negative predictive value, 94% in the classification of OMI patients and normal controls. The processing time is less than 5 seconds per one subject. It suggests a possible application of the proposed method in mass screening of abnormal MCG patterns.

KEY WORDS

magnetocardiogram, excited wave front, myocardial infarction, screening, wavelet approximation, Gaussian mixture modeling, Bayes criterion

INTRODUCTION

MCG provides visualized electrophysiological field maps of the heart, and is considered as potential complementary and substitutive methods for electrocardiogram (ECG). To further utilize the advantage of non-contact registration and noninvasive measurement in clinical application, MCG should be used for an initial medical checkup. Therefore, we are developing a mass screening method to automatically distinguish abnormal patterns of cardiac excitation by using MCG. In this paper, we propose a Bayesian classification method with newly developed parameterization techniques of magnetic field maps. The Bayes rule is a classifier that minimizes an error rate of false positive and false negative, and is one of widely used algorithms of pattern recognition [Christopher, 1995a]. The difficulty in applying the Bayes theorem to MCG classification is the parameterization of magnetic field maps. Data of a MCG field map in even one time window consists of tens of values of magnetic flux density that were measured at the respective measurement sites. In order to track the excitation pathway during one heart cycle, the magnetic field maps of more than a hundred analyzing time windows should be processed at once. We newly developed two-dimensional wavelet approximation and cluster analysis techniques to parameterize the magnetic field maps into a simple indicator, and applied it to the Bayesian classification of OMI patients and normal controls.

METHODS

MCG data used in this study. MCG examination was conducted on the MCG system (Hitachi Ltd., [Tsukada, 1998]) at the Institute of Clinical Medicine, University of Tsukuba, Japan. The system has 8 x 8 SQUID (Superconducting Quantum Interference Device) magnetometers at intervals of 2.5 cm in a 17.5 x 17.5 cm² measurement area. MCG data of 6 patients with OMI (2 inferior, 2 posterior, and 2 anteroseptal infarction) and 15 normal controls were taken at a sampling frequency of 1 kHz through a 0.1-100 Hz band pass filter and a notch filter of the power line frequency of 50 Hz. The data were off-line processed to an averaging more than 20 times at the points of R peaks in simultaneously measured ECG on the second lead, and baseline correction. Coronary angiography was carried out to determine the area of the infarction in the patient with OMI. Clinical diagnoses of the normal controls were based on 12 lead ECG. In the analysis, we used the magnetic field maps of the repolarization phase (ST-T period) that corresponds in the last one third of the time course between the peaks of R wave and T wave.

Classification method. The classification method consists of two procedures of MCG field maps parameterization ((a), (b)), followed by the Bayesian classification of the parameter (c), as shown in figure 1.

(a) The 'wave front vector' is defined from the magnetic field map of an analyzing time window. Using the wavelet approximation, we choose positions at which a magnetic field map gives a positive and a negative spatial extreme points. The cardiac excited wave front is considered to exist in the plane that is perpendicular to the chest and contains the line that connects the positive and negative extreme points. Therefore, we defined the position and the direction of the wave front vector as the center of these extreme points and the direction perpendicular to the direction from the positive extreme point to the negative extreme point, respectively (See figure 2). The wave front vector interprets the coronal center position and the travel direction of the excited wave front. The detail of the determination procedure is mentioned in our previous report [Ono, 2002].

(b) The subject's wave front vectors through all the analyzing time are summarized into a 'cluster pattern', which is used for Bayesian classification. Since the number of the wave front vectors amounts to more than a hundred with each subject, it is not suitable to directly apply the Bayes theorem to the wave front vectors. The wave front vectors of all the subjects were divided into some clusters in advance. Using Gaussian mixture modeling (GMM) with expectation maximization algorithm [Christopher, 1995b], we applied 5 Gaussians model to the all wave front vectors in this study. As shown in figure 3, hereafter we describe these 5 clusters as $C_1, C_2, \dots, C_5$, respectively. Then we determined the cluster pattern of a subject according to the distribution of

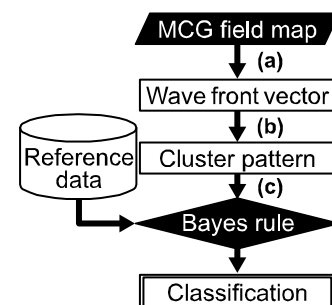


Figure 1. Flow chart of Bayesian classification of MCG.

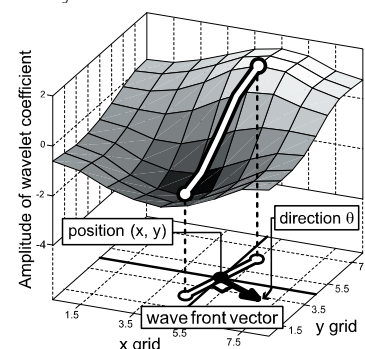


Figure 2. Determination of wave front vector.

his / her wave front vectors among the clusters. The Mahalanobis distances between the wave front vector and the mean position of the respective clusters are calculated, and the wave front vector is classified to the cluster that has the shortest Mahalanobis distance. All of the wave front vectors of a subject in the analyzing time windows are classified in this way. The cluster pattern (*k-l*) indicates that the population of the wave front vector in the cluster *C_k* is the largest and that in the cluster *C_l* is the second largest. If all of the wave front vectors are classified into one cluster *C_k*, the cluster pattern is (*k*). The Mahalanobis distance is used to take the trends of variance and covariance of the respective clusters into account. In order to apply the Mahalanobis distance, the cluster should be Gaussian distributed. Therefore we used GMM in the cluster analysis. We used the following equation (1) to calculate the Mahalanobis distance:

$$d_i = \sqrt{(\mathbf{x} - \mathbf{m}_i)^T \Sigma_i^{-1} (\mathbf{x} - \mathbf{m}_i)} \quad (1)$$

where *d_i* denotes the Mahalanobis distance between the wave front vector **x** and **m_i**, the mean position of the cluster *C_i*. And **Σ_i⁻¹** represents the inverse of the covariance matrix of *C_i*.

(c) The conditional probability of the parameter to belong to patient or normal group is estimated by the Bayes theorem. The Bayes theorem given in equation (2) predicts the probabilities of a subject to belong to the respective groups to classify.

$$P(A_k | B) = \frac{P(A_k)P(B | A_k)}{\sum_{i=1}^s P(A_i)P(B | A_i)} \quad (2)$$

where {*A_k* | *k*= 1, ..., *s*} ⊂ *A*, *P*(*A_k*)>0. In this case *A_k* means the group of inferior OMI (*G_i*), anterior OMI (*G_a*), anteroseptal OMI (*G_s*), or normal (*G_n*) and *B* means the cluster pattern. The probability density of a subject belonging to each of the group *A_k* is denoted as *P*(*A_k*). And the probability density that a subject has the cluster pattern *B* given that the subject belongs to the group *A_k* is denoted as *P*(*B*|*A_k*). The conditional probability *P*(*A_k*|*B*) that a subject belongs to the group *A_k* given that his / her cluster pattern is *B*, is estimated with these prior probabilities of *P*(*A_k*) and *P*(*B*|*A_k*). The estimated conditional probabilities for the cluster pattern to belong to the groups of *G_i*, *G_a*, *G_s*, and *G_n* are indicated in table 1. In the application of the Bayes rule, the probability belonging to *G_n* and the sum of the probabilities belonging to *G_i*, *G_a*, and *G_s* are compared. And each subject is classified into Normal / OMI group when the former / latter probability is larger.

Table 1. Cluster pattern (CP) and the corresponding Bayes rule.

CP	Estimated probabilities				Bayes rule
	OMI			Normal	
	<i>G_i</i>	<i>G_a</i>	<i>G_s</i>	<i>G_n</i>	
1	0%	0%	0%	100%	Normal
2	0%	0%	0%	100%	Normal
5	0%	50%	50%	0%	OMI
2-3	100%	0%	0%	0%	OMI
2-4	0%	34%	0%	66%	Normal
3-4	50%	0%	50%	0%	OMI

Table 2. Clinical diagnosis and classification result.

Classified \ Diagnosed		
	OMI (+)	Normal (-)
OMI (+)	5	0
Normal (-)	1	15

Table 3. Positions of coronary artery stenosis and cluster pattern. Abbreviation; Inf. (inferior), Ant. (anterior), Ant. sep. (anteroseptal).

Sub ject	Infarction area	Stenosed position (AHA)				CP
		#1	#3	#6	#7	
p1	Inf.	90%	100%			3-4
p6	Ant. sep.	99%	75%		99%	3-4
p3	Ant.			90%	75%	5
p5	Ant. sep.			90%	90%	5
p2	Inf.		100%		75%	2-3
p4	Ant.	100%			75%	2-4

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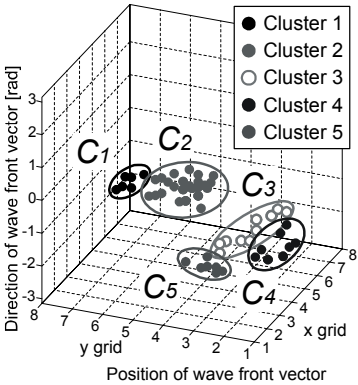


Figure 3. Clusters of wave front vectors.

RESULTS

The result of the classification of OMI patients and normal controls is shown in table 2. The method showed sensitivity (the percentage of patients recognized by the method) of 83%; specificity (the percentage of normal controls recognized by the method), 100%; positive predictive value (the percentage of patients among the subjects who are classified as positive (OMI) by the method), 100%; and negative predictive value (the percentage of normal controls among the subjects who are classified as negative (Normal) by the method), 94%, respectively. The total calculation time to classify a subject from the MCG data was less than 5 seconds with MATLAB software on a personal computer (1.8 GHz Intel Pentium4 CPU with 1GB RAM). Note that we used the same MCG data for classification as well as for the definition of clusters of wave front vectors and Bayes rule since we had small samples. In the practical use of this method, the clusters and the Bayes rule should be defined beforehand with large samples and new MCG data should be classified with it.

DISCUSSION

The difference in the characteristics of the excited wave fronts among patients and normal controls was clearly distinguished by the cluster patterns. As shown in table 1, the excited wave fronts of OMI patients during the repolarization phase had tendency to exist in the different position and direction from those of the normal controls. In myocardial infarction, the excited wave front may be obstructed and diverted when passing the infarction area. It is thought that this change in the pathway of excited wave fronts caused the different distribution of the cluster pattern in OMI patients. In addition, the cluster pattern of OMI patients had a good correlation with the positions of artery stenosis that was examined by coronary angiography, as shown in table 3. The result suggests the possibility of MCG in the screening of stenosed position of arteries. In summary, the use of the presented techniques is acceptable to the practical mass screening with the short processing time. Future studies should also evaluate the capability of the presented method with larger samples.

Multiple-channel SQUID System with Referential Sensors for Magnetocardiography

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ABSTRACT

We have developed a multiple-channel SQUID system for the measurement of magnetocardiograms.

This 64-channel SQUID system has 1st-order gradiometers and low-T_c dc-SQUIDs as magnetic sensors (Hitachi High-Technologies Co., Ltd.). These sensors are set in 8 × 8 array in 175 × 175 mm². The FRP dewar can store of 46 L liquid helium and evaporation rate to 7 L / day. A magnetically shielded room was made by permalloy - aluminium - permalloy layers, withan inner space of 2300 mm (W) × 1900 mm (D) × 2300 mm (H). Under clinical conditions, the magnetic shielding effect is over 30 dB at 0.01 Hz, over 33 dB at 0.1 Hz, over 45 dB at 1 Hz, over 65 dB at 10 Hz ~. The residual static magnetic field is less than 1 mG. The driving circuit FLL uses unmodulated system based on a Drung method. The feedback current is monitored for a digital value, it brings resistance to dynamical change of the field.

This system built with 12 reference sensors placed 50 mm upward from main sensors. These references allow the reconstruction of 2nd-order gradiometers with 64-channel sensors, combining linear function with weight parameters. This referential system is advantageous to MCG work at clinical conditions and when analyzing small signals.

KEY WORDS

magnetocardiography, instrumentation, multiple-channel SQUID

MULTIPLE-CHANNEL SQUID SYSTEM

SQUID :

This 64-channels SQUID system was constructed from 1st-order gradiometers and low-T_c dc-SQUIDs as magnetic sensors (made by Hitachi High-Technologies Co., LTD). These sensors have a magnetic field sensitivity under 18 fT/√Hz. The environmental field is reduced by using a Nb shield at each SQUID device. The pickup-coil of these sensors has a diameter of 17.8 mm and 50 mm baseline formed on the PPS resin bobbin designed for the measurement of cardiomagnetism. These sensors were seated in an 8 × 8 array at intervals of 25 mm. It has an observation area of 175 mm × 175 mm at one time measurement (Figure 1).

In addition, 12 reference sensors were placed 50 mm upward from main sensors. These references were used to reconstruct 2nd-order gradiometers with 64-channel sensors, combining linear function with weight parameters.

The driving circuit, FLL :

This 64-channels SQUID system has detached FLLs for each sensor that is seated in aluminum box, 30 mm (D) × 45 mm (W) × 50 mm (H) (made by Kansai Research Institute, Inc.). The sampling rate is 500 Hz. This driving circuit FLL uses an unmodulated system based on a Drung method. The feedback current is monitored for a digital value, it brings resistance to dynamical change of the field.

Cryostat (Dewar and Insert) :

The cryostat was constructed with FRP dewar and FRP insert. The volume of this dewar is 46 L and evaporating rate of the liquid helium is 7 L/day. Thickness of a vacuum insulation is less 25 mm and it contains three layered thermal shields. The insert has spring to prevent the vibrations of the SQUIDs.

The Magnetic Shielding Room :

The magnetically shielded room was made of permalloy - aluminum - permalloy (Takenaka Co., Ltd.). It has a inner space of 2300 mm (D) × 1900 mm (W) × 2300 mm (H). The magnetic shielding effect is over 30 dB at 0.01 Hz, over 33 dB at 0.1 Hz, over 45 dB at 1 Hz, over 65 dB at 10 Hz~. And the residual static magnetic field is less than 1 mG in this room. The total system noise showed in Figure 2.

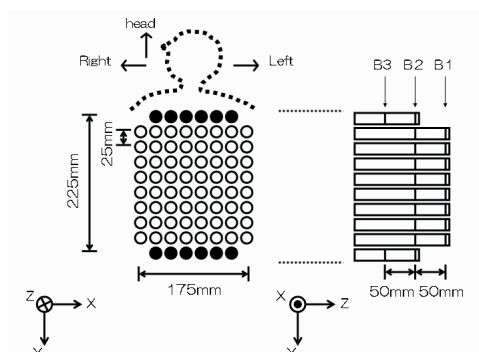


Figure 1 : Arrangement of SQUID sensors. White circles: main sensors, Black circles: reference sensors.

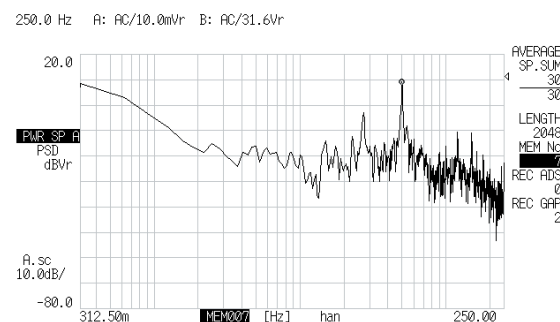


Figure 2 : The system noise of the 64-channel MCG it is 68 fT/√Hz at 10 Hz under clinical conditions.

EXPERIMENTAL SECTION

The 2nd-order gradiometer signal was constructed from the 1st-order gradiometers, $B_z = (B1 - B2) - (B2 - B3)$, $B1$, $B2$ and $B3$ are the magnetic field, show in Figure 1. 12-channel references supplied 64-channels 1st-order gradiometer over the main sensors using a function with weight parameter as $s'(t) = [T] s(t)$ ($s(t)$; matrix of 12-channel reference signals, T ; weight parameter, $s'(t)$; matrix of 64-reference channel signals as $B2 - B3$). In this study, we attempted to eliminate noise in the signal from 64-channel main sensors by 12-channels references. Figure 4 shows result of the effect of noise elimination on the one channel by reconstruction the 2nd order gradiometers.

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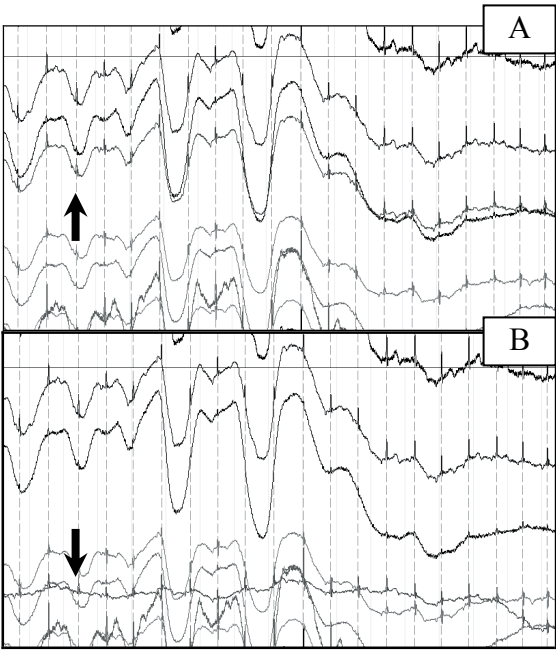


Figure 4 : Results of noise elimination for the 1ch-MCG signal (see the arrows in this figure). Random magnetic noise were induced by shaking of magnetic metal.
A : before applying the effect.
B : after applying the effect.

MCG: New Insights into Old Ideas

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ABSTRACT

Presently is the right time to finally attain the answers that MCG technology can best provide. MCG has been around for over 30 years but it remains difficult to present MCG as an extremely effective clinical diagnostic tool to obtain additional insight into the heart. This is the reason why we are often confronted with the following questions: Why do scientists continue to develop MCG when so many alternative tools are available? Why has it taken so long? What is the current framework for the future prospects of MCG-technology?

The result of the recent studies, which can provide certain framework for the current-structure interaction in the ventricular wall and can be interpreted through MCG-data, can be stated with three general observations: (1) The established fact is that electrophysiological properties of the ventricular myocardium are extremely heterogeneous. (2) Major advances were made in understanding that the myocardium can not be considered electrically as a continuous medium. (3) A direct and specific relationship between cellular ionic processes and the APD.

KEY WORDS : Magnetokardiogram ; Repolarization; Current density; Ionic processes.

INTRODUCTION

Presently is the right time to finally attain the answers that MCG technology can best provide. [Malmivuo,2003] stated “The theory of bioelectromagnetic measurements and the relationship between the ECG and MCG are finally understood”. Yet a few years before [Brockmeier,1997] still wrote “It is too early to give a physiological interpretation of the repolarization behaviour of the MCG”. How can these 2 opposing statements be reconciled?

MCG has been around for over 30 years but only recently the significant progress in instrumentation has increased the interest in the use of MCG in clinical cardiology. All these years numerous theoretical and experimental research have been conducted on the quantitative estimates of the sensitivity and specificity MCG-method applied to various cardiac disorders. However, it remains difficult to present MCG as an extremely effective clinical diagnostic tool to obtain additional insight into the heart. This is the reason why we are often confronted with the following questions:

WHY DO SCIENTISTS CONTINUE TO DEVELOP MCG FOR DIAGNOSING CARDIAC DISORDERS WHEN SO MANY ALTERNATIVE TOOLS ARE AVAILABLE?

It is known that the current density and magnetic field are related by the law of Biot and Savart. That means, that the information about the current density source distribution should be present in a measured magnetic field. Using SQUID technology for measuring the magnetic field of the heart we gain a unique opportunity to identify changes in the current density that constitute the basis of the myocardium electric activity. The first motivation for scientists is to visualize the distribution pattern of the current sources and to clarify how well these representations reflect the reality. The second motivation is to answer the question: “Whether or not MCG-study can add something new to the diagnostic information gained from the standard clinical tests?” And, then, which of the methods can be chosen as the reference? The diagnostic performances of many currently available techniques show that they cannot reflect the data that MCG is capable of recording.

WHY HAS IT TAKEN SO LONG ?

The answer to the second question requires a more detailed analysis of the current status of the MCG-technology. It is necessary to note that significant progress in the electronic MCG signal imaging technology, both in terms of hardware and software, as well as mathematical and physical modeling over the past 10 years have made for the turning point. The new methods of the data analysis and effective technical solutions were applied during numerous clinical examinations. However, the scientific efforts have not been very successful because the clinical examinations which were gathered over the past 15 years have not convinced practicing cardiologists that the MCG-technology is “the best, and most likely, the only solution”. The reason can be explicated with two general observations. On the one hand, previous extensive investigations were devoted to the analysis of the features of the magnetic field map (MFM). However, the results of this analysis were subject to the influence of the correlation among the signal-to-noise ratio of the measured magnetic field, the distance between the current source and the position where the magnetic field is measured, the size of the magnetometer and the large diversity of maps secondary to biological variability. The reconstruction of the current density distribution (CDD) by means of the “inverse problem solution” was the most significant step to reduce the influence of the above mentioned factors and to visualize the electrical events inside a rather large volume of the myocardium. On the other hand, the main question not yet solved is: what phenomenon in myocardium electrophysiology is mapped by some MFM or CDD abnormalities? There exist strong evidence that the electrophysiological behavior of the heart may be altered in ischaemia which causes abnormal MCG-mapping patterns during the repolarization phase. MCG-map abnormalities were detected in all patients with severe coronary lesion. It is remarkable that the magnetic map changes in ventricular repolarization can be observed as early as in the results of healthy subject measurements during physical exercise or pharmacological stress. In the study by [Brocumeier, 1997] the dramatic influence of increased heart rate on repolarization mapping patterns was found for healthy volunteers. In contrast to MCG, significant stress-induced differences were not observed in ECG and BSPM - recordings. Many authors agree on that “abnormal” mapping patterns are “the special properties of MCG such as the ability to detect so-called vortex currents (loop currents, injury currents)”. Helmholtz theorem, which decomposes a vector field into the flow and vortex parts was the theoretical basis for interpretation of the magnetic map changes. Discussion that the information about myocardial electrical phenomena can be present in the biomagnetic field and absent in the electrical field have been well known since very first MCG measurements. Opportunity to display the “electrically silent” magnetic field was demonstrated in theoretical study [Roth,1986] with the example of the tissue that has a “spiral-like” or “helix-like” conductivity. However, authors pointed out that it is not clear if such strands occur in nature. Simulation study by [Fisscher,2001] showed that vortex components of the magnetic field are much smaller than the flux source field and should be detectable “in principle”, but authors stressed that “there were always some doubts

regarding the existence of a vortex field". In such important aspects as tissue anisotropy and discontinuities in tissue structure the myocardium is different from the generic excitable media typically considered in the theory of vortex currents. In the electrophysiological view, the origin of the vortex loop currents during repolarization in the case of the increased heart rate is poorly understood, and no experimental data are available in the literature regarding the ionic mechanisms of vortex loop currents in biological tissues. So far as a physiological interpretation of the depolarization and the repolarization behavior in the MCG has not been offered, it will be difficult to dislodge the opinions of clinical cardiologists that easily available techniques can be successful alternatives to MCG.

WHAT IS THE CURRENT FRAMEWORK FOR THE FUTURE PROSPECTS OF MCG-TECHNOLOGY ?

Cardiac electrical specialization has been studied for over 100 years, but how specialization is achieved by differential expression of ion channels has been learned only over the last 10 years. The result of the recent studies, which can provide certain framework for the current-structure interaction in the ventricular wall and can be interpreted through MCG-data, can be stated with three general observations.

1. The remarkable and established fact is that electrophysiological properties of the ventricular myocardium are extremely heterogeneous and dispersion of repolarization may be an important factor that determines the manifestation of the heterogeneous ion channel function and expression. A variation in action potential duration (APD) creates the dispersion of repolarization and the baseline level of APD differences exists even in a normal myocardium.

2. Major advances were made in understanding that the myocardium cannot be considered electrically a continuous medium. It has become accepted that the myocardium is structured to discontinuous activation and recovery. There are numerous previous studies available in the literature that suggested the effect of myocardial fibers geometry on the current flow patterns, epicardial and torso potentials. A key feature of this anisotropic arrangement is that transmural rotation of fibers and the laminar architecture of the ventricular wall can affect electro-potential and magnetic data.

3. The modeling study by [Kazutaxa Gima, 2002] establish a direct and specific relationship between cellular ionic processes, the APD, and the morphology of electrocardiographic wave forms. The results show that transmural slow-delayed rectifier potassium current heterogeneity is the major determinant of T-wave morphology and the spatial gradient of the transmembrane potential during repolarization is determined by two factors: sequences of activation and local APD.

Based on this latest knowledge we can assume that the heterogeneity of an action potential is caused by an intramural heterogeneity of a current flow and for each time instant a result of the "inverse problem solution" can display a resulting current density vectors, whose quantity and direction correspond a quite particular allocation of outward current densities at a certain level (depth) and reflect the architecture of the fiber through which the current propagates. The discontinuities in tissue architecture and different pathological conditions can affect this electrical heterogeneity. Several studies reported that the density of the transient outward current may be subject to alterations during ischemia, in cardiac hypertrophy or failure, after myocardial infarction. That is why our focus should be on the ionic mechanisms that contribute to the intramural nonuniformity of cellular repolarization at certain depth of myocardium and on intramural current heterogeneity as a basis for identifying patients at risk and for evaluating the effects of intervention (eg, drug treatment) on the degree of heterogeneity. A frequent change of the direction of the current densities vector may be interpreted as a high degree of heterogeneity inside a certain tissue region. A local shortening of the current flow duration in the area of abnormal perfusion can be an independent marker of early localized myocardial ischaemia. It appears therefore that myocardial perfusion scintigraphy, which demonstrated a good correlation between the APD changes and the location of the ischemic areas, can be chosen as the acceptable reference method. The principles stated above fully correspond several clinical MCG examination sessions comparing healthy individuals against patients with a normal resting ECG or unspecific changes of ventricular repolarization.

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Functional Anisotropy: can it be detected by Magnetocardiography?

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ABSTRACT

The registration and the evolution of the angle between the direction of the electro-motive force and the direction of the current density vector from frontal plane projection of the human heart were calculated by means of specially designed software. The electrical processes in myocardium are displayed as sources of the electrical activity with specific current densities. The local change in density and direction of ion currents might be characterized as a functional anisotropy. The MCG provides an opportunity to detect a functional anisotropy manifestation as a marker of the underlying heart disease which has not yet manifested itself clinically.

KEY WORDS: Magnetocardiography; current densities; anisotropy

INTRODUCTION

With recent developments in the technology of Magnetocardiography (MCG), which now make it possible to measure the human magnetic field without special shielding during myocardial de- and repolarisation, an old issue has resurfaced: Can suspected anisotropy be better detected by this modern technology? The answer to this question relates to the understanding of the ionic origin of cardiac excitation. There are several sources of anisotropy which may lead to the non-homogeneous spread of excitation: the human myocardial fibre orientation with its unique spiral construction, the conduction disturbances secondary to ischemia or other metabolic disorders, and the degree of fibrous scar formation as a remnant of coronary artery disease to name but a few. A MCG signal is a reflection of a system of currents distributed in a plane, parallel to the measurement plane. The goal of this study was to investigate whether the orientation of ion currents provide independent diagnostic information.

METHODS

The standard 12 lead ECG from 18 healthy volunteers was obtained immediately before the MCG and under resting conditions. Heart rates were virtually identical at each examination. The ECGs were read by an expert, unaware of the MCG result, and deemed to be normal in all 18 healthy subjects, as well as in the 32 patients with angina. Coronary artery disease was angiographically determined with at least one stenosis $>75\%$ in ≥ 1 vessel. Angiography was carried out before the MCG was recorded. After measurement of the ECG the direction (α) of the electro-motive force (EMF) vector in frontal plane was calculated at the R-, T-peaks and at other times during the cardiac cycle.

MCG was obtained with a 4-channel system (MCG-7, SQUID AG, Essen) in an unshielded setting. Current density vector (CDV) maps were plotted from the "inverse problem solution", which was formulated as follows: the field source is a 2D system of currents situated in the plane parallel to measurement plane from which the spatial configuration of the currents producing the magnetic field is derived [Primin, 1998].

The present study is based on the assumption that anisotropy, if present, is characterized by an angle γ , between direction (α) of a EMF vector projection and direction (β) of an CDV projection in frontal plane of the human heart at the same time

$$\gamma = \alpha - \beta.$$

CDV is vector sum of the elementary CDV of all myocardial cells, which are active. The angle γ between the direction of the EMV and the direction of the CDV from frontal plane projection of the human heart was calculated.

RESULTS

In Fig. 1 the results are shown of the anisotropy angle measurement for the 32 patients with CAD with unchanged resting ECG and 18 healthy volunteers. In the healthy subjects, the angle γ at the R- peak is 22.0 ± 3.60 (mean value standard error), while for CAD patients it is 47.50 ± 6.30 .

For the peak of the T-wave these values are respectively 19.20 ± 5.80 and 50.0 ± 6.0 . Also at other time moment of the cardiac cycle significant differences were found between the CAD patients (RIVA stenosis) and the volunteers (Fig.2).

DISCUSSION

The activation and recovery waves spread across an excitable medium that constitutes an anisotropic and discontinuous structure. The structural features can affect local current flow direction. In the human myocardium the driving force for ion current flow consists of 2 components: electromotive and thermodynamic driving forces. Thus local changes in the myocardium ion transfer are not always accompanied by changes in the potential difference as reflected in the action potential. The real influence of the geometrical factors and the exact nature of a ionic driving force should be demonstrated by measuring data from living intact organ. Recent animal experiments with induced regional and temporary ischemia, have also demonstrated rapid changes in the MCG not seen in the surface ECG until much later when ischemia was more pronounced or had actually induced necrosis. It has been proved that current density differences contribute significantly to regional electrophysiological heterogeneity and to cause electrical gradients across the ventricular wall [Näbauer, 1996]. The electrophysiological behavior of the heart may be altered in disease, presumably by changes in individual ion currents or disease-induced increased ion channel density. The electrical processes in myocardium are displayed as sources of the electrical activity with specific current densities. The most wide-spread reason of infringement myocardial function is an inadequate oxygen delivery, resulting in imbalance between oxygen demand and energy supply. Several adaptive mechanisms can initially preserve myocardial cellular survival during temporary hypoxia. Such anaerobic cell metabolism, if severe enough, will lead to local change in density and direction of ion currents. This process we can characterize as a functional anisotropy.

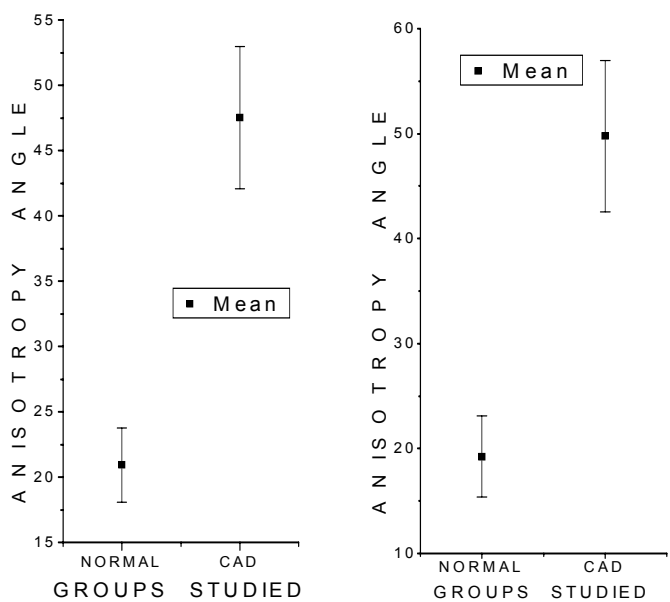


Fig. 1. . Mean ±SE values of angles γ : left) R-peak, right) T-peak.

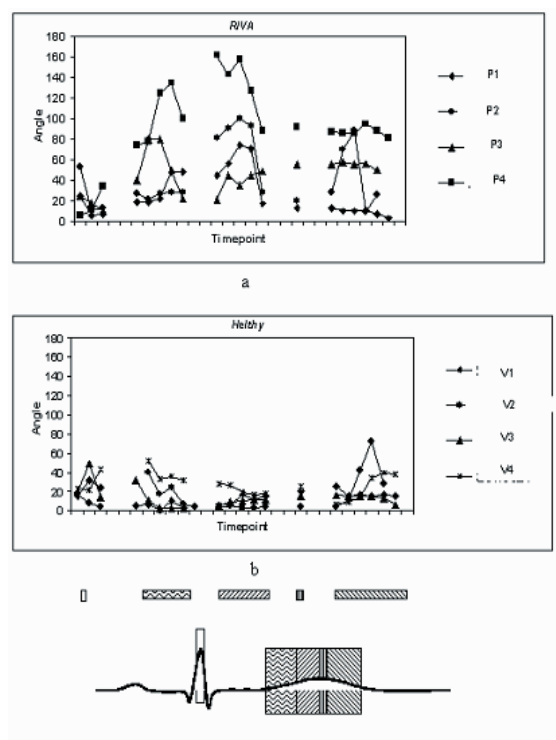


Fig. 2. The typical quantities of a angle γ are shown on different time moment of the cardiac cycle for groups of the patients P1,2,3,4 (a), the volunteers V1,2,3,4 (b).

In the human it has been shown by [Malmivuo ,1994] that the difference between the electric heart vector (EHV) and the magnetic heart vector (MHV) at the R peak of the QRS complex is very close to 90° when conduction is normal. In fact , it should be identical. However , various authors have found an angle quite different from 90° between patient groups and in various cardiac disorders. On the other hand , [de Torbal ,2004] concluded that the frontal T-axis and QRS-T angle provide independent diagnostic and prognostic information. [Sachse,1997] demonstrated in a realistic impedance model of the human torso the electric potentials to be sensitive to heterogeneous and isotropic conductivity but not to anisotropy. Therefore , it appeared attractive to measure the angle between the direction of the EMV and the direction of the CDV in frontal plane projection of the human heart. The best insight in the source of the bioelectromagnetic fields can be obtained when both the electrical and the magnetic field are measured in the same individual , thus excluding individual differences in anatomic structures and the variability in the biochemical origin of the ionic driving.

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Spatial distribution of cardiac magnetic vector fields acquired from 3120 SQUID positions

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ABSTRACT

An extended measurement of the vector field of the human heart is presented. It is acquired by sequential recordings, shifting a 16 SQUID vector magnetometer across 195 positions over a healthy subject's thorax. The MCG signals were synchronized using a simultaneously measured ECG channel. The registration of the field extends over a volume of 1000 mm x 600 mm x 420 mm sampled at 3120 SQUID positions. We present diagrams of the the vector amplitude of selected points in 6 planes at increasing distances from the frontal thorax. Each plane contains 76 vector points. Additionally, we measured the vector field at 126 points lateral to the chest. At the edge points of the measurement volume, the absolute value of the magnetic vector signal amplitude exceeds 0.3 pT in all measurement points.

The dataset provides an excellent base to study dedicated MCG detection or rejection methods. Examples where rejection of the heart signal is necessary are MEG, MNG and fMCG. The knowledge of the spatio-temporal distribution of the magnetic vector field of the heart supports the development and comparison of multi-SQUID systems and will be used to create new MCG interpretation and representation algorithms.

KEY WORDS

Vectorcardiography/methods, Magnetics/diagnostic use/instrumentation, Heart/physiology/physiopathology

INTRODUCTION

The present work describes the acquisition of the human cardiac magnetic vector field in an extended volume over the thorax. The magnetocardiogram (MCG) has been extensively used to characterize the electric heart activity in normals and patients with different heart diseases. Many MCG systems measure one component of the magnetic vector field or its gradients in a plane over the thorax. Other MCG systems, commonly referred to as vector systems, were designed to acquire different spatial gradients of the magnetic field [Wikswa 1975, Nousiainen 1994a, 1994b, Drung 1995, Kobayashi 2000]. We previously described a SQUID system with the capability to estimate all three magnetic field components at one point [Burghoff 1999]. Here, we used a similar vector system, described in detail elsewhere in this volume [Burghoff 2004], to map the magnetic vector field over the thorax.

The detailed knowledge of the cardiac magnetic field structure may serve different purposes:

- It provides better constraints for methods aimed at the non-invasive characterization of cardiac electrophysiology, both for inverse methods [Nenonen 2001] and field parameterization [Kobayashi 2002].
- It provides data that can be used to improve special MCG sensor configurations [Kandori 1996].
- It provides information for effective noise cancellation methods in biomagnetic measurements of other organs, where the MCG is considered an artifact [Sander 2002].
- It helps to develop more intuitive representation methods of magnetic field data [Burghoff 1999].
- It allows to check methods for converting the data between different MCG systems [Burghoff 2000], since all gradiometer types can be derived from the complete data set.

METHODS

The magnetocardiogram of a healthy volunteer was acquired in the magnetically well shielded room BMSR 2 at PTB. The used vector system combines 16 SQUID magnetometers that measure in their combination all three orthogonal magnetic field components at three different points on a line along the z-axis. For a detailed description, we refer to another contribution in this volume [Burghoff 2004]. The vector system was shifted to 195 positions over the thorax. The layout of the measurement grid was the following:

- An 11 x 7 plane in x-y with a grid spacing of 100 mm both in x- and y-direction. The distance of the nearest vector point in that position to the thorax surface was approximately 260 mm.
- Another plane as described in 1.), shifted 140 mm along the z-axis towards the thorax surface. The distance of the nearest vector point in this plane to the thorax surface was approximately 120 mm.
- Two rows of 7 positions at each side of the body shifted 140 mm from plane 2.) along the z-axis towards the soil.
- One row at each side of the body shifted 140 mm from the outer rows in 3.) along the z-axis towards the soil.

For technical reasons, one position in each of the setups 1-4 could not be evaluated. The setup is shown in Figure 1.

The MCG signals were measured in each position for 20 seconds. The subject's position was stabilized by the use of a vacuum mattress. The total measurement time was approximately three hours. Additionally to the MCG, one ECG channel was acquired simultaneously in every position. The ECG was used to synchronize all MCG measurements [Jazbinsek 2001]. For that purpose, similar QRS complexes in the ECG channel of all positions were selected by a cluster analysis. In the case of multiple similar beats per position, the MCG data were averaged.

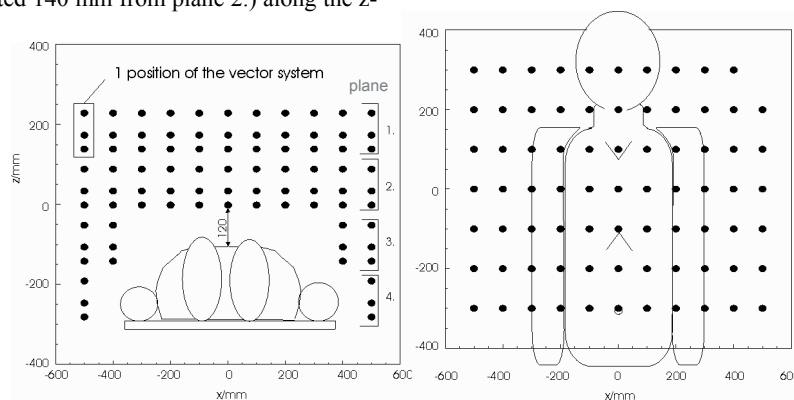


Fig.1 Schematic drawing of the vector positions in the x-z and x-y plane.

The averaged MCG signals from all positions were then synchronized in time according to the best correlation in the ECG channel and combined to form a large virtual MCG sensor. The combined data set includes 195 system positions with 16 SQUIDS at each position, a total of 3120 measuring positions for the SQUIDS. After a careful definition of a baseline point before the onset of the P-wave, we calculated $195 \times 3 = 585$ magnetic vectors, each vector is characterized by its B_x , B_y and B_z components.

RESULTS

The cardiac magnetic field could be observed in all SQUID positions, even in a distance of >600 mm. While the largest observed vector amplitudes were approximately 24 pT, the smallest field vector amplitudes at the edges of the measurement volume amounted to ~ 300 fT. The vector components B_x , B_y and B_z over the total measurement volume are in the same amplitude range, but exhibit different spatial patterns. The distribution of the vector amplitude $|B|$ in the planes $x=0$ and $y=0$ is shown in Fig. 2. We created movies of 3D-representations of the vector field as it was proposed in [Burghoff 1999]. An example is shown in Fig. 3, depicting the vector field at QRS maximum, seen from the head towards the feet.

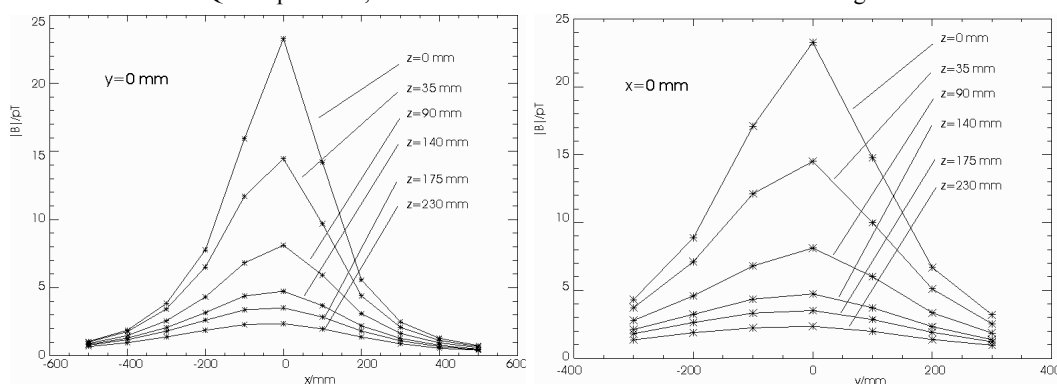


Fig.2. Dependency of the vector amplitude $|B|$ on x and y in different distances from the thorax.

Fig.3. 3D representation of the vector field during QRS maximum. View from subject's head.



DISCUSSION

We created a unique data set describing the cardiac magnetic vector field in large volume over the heart. This data represent a valuable resource for method development in SQUID systems design, MCG research and other biomagnetic techniques where the MCG is considered an artifact. The availability of complex vector information boosts the development of new techniques for data handling and representation. The use of vector systems with large numbers of sensors [Schnabel 2004] will allow real simultaneous acquisition of the magnetic field in a large volume, thereby further increasing the data quality.

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MCG as a Tool for Drug Safety Testing and Knock-Out Model Animal Studies

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ABSTRACT

Recent drafts issued by American and European regulatory bodies require to test the safety of all medical drugs with respect to the drug's potential to cause heart arrhythmia. These safety pharmacology studies include the evaluation of QT interval prolongation in animals. Other studies performed on knock-out animals require the assessment of electrophysiological changes due to gene alterations. Magnetocardiography (MCG) as a contact-free measurement method is an excellent tool to perform such animal studies. We measured high signal-to-noise ratio MCGs from mouse, guinea pig, rabbit and hamster. The maximum field amplitudes are in the order of 3 pT. This allows the analysis of heart rate, heart rate variability and of QT intervals in the averaged heart beat. High quality signals were easily obtained from non-anesthetized animals, a big advantage compared to ECG or other methods. Since no special preparation time is required, the measurements can be performed with a high through-put. Additionally, we present an outline of the construction of a specialized animal MCG system. It consists of a dewar with a room temperature hole for the animals and SQUIDS in a circular arrangement around the hole. The superconducting magnetic shielding made of niobium is integrated to the dewar to enable measurements outside a magnetically shielded room.

CONCLUSION: MCG provides heart rate, QT interval and other parameters from small animals, even not anesthetized, in a fast and reliable way. The construction of special animal MCG system will allow high through-put studies for drug safety testing and screening of genetically modified animals.

KEY WORDS

Magnetocardiogram, drug safety, QT interval, animal electrophysiology, biomagnetic equipment

INTRODUCTION

We propose the use of multi-channel magnetocardiography for animal studies on QT intervals and for the characterization of gene knock-out animals. Concerns about prolongation of the QT/QTc time and subsequent initiation of torsade de pointes arrhythmias have become a major cause for drug withdrawals or refusals. This situation has boosted worldwide efforts to harmonise safety tests for newly approved drugs with respect to their proarrhythmic potential. Guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) titled S7B - Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals [ICH 2002] and E14 - Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs [FDA 2002] are in a mature state.

The implementation of these guidelines by regulatory agencies will lead to a large number of QT/QTc measurements in pre-clinical and clinical phases of drug design and approval. Both the safety of future drug users and economic considerations of pharmaceutical companies call for the highest possible accuracy and reliability of QT/QTc data. High throughput QT determination methods are needed to create the database for a statistically sound drug safety analysis. Standard 12-lead ECG is now recommended as a compromise between labour intensity and information content. However, electrode placement errors and changing electrode-skin contacts might influence the ECG quality and lead to erroneous QT intervals. The feasibility of QT measurements in the rat MCG has been recently demonstrated by Brisinda and co-workers [Brisinda 2004]. The ICH guidelines refer explicitly to the use of in-vivo tests using telemetry in animals before the initiation of a clinical study. We demonstrate the easy measurement of QT intervals in conscious unrestrained small animals by MCG.

The growing possibilities of creating gene modified animals generates the need for the characterization of the phenotype changes in such animals. The MCG, offering fast high throughput measurement capabilities, is a well suited tool to perform such studies. Recently, special MCG devices for animal research have been developed and used for characterization of cardiac ischemia in rats [Uchida 1999, Kwon 2001]. Here we present the concept of a SQUID system with integrated superconducting niobium shield. Such a system might be used for studies on genetically modified mice, a widely used animal for gene knock-out studies. The MCG of a mouse could be measured using a high-T_c SQUID system [Ludwig 2001].

METHODS

We used a 16-channel vector MCG system to measure a rabbit, a guinea pig and two hamsters in conscious unrestrained state. A mouse MCG was acquired using a high-T_c SQUID system. The animals were handled according to the German Animal Welfare Act (Tierschutzgesetz). Only a minimal preparation was required for the conscious animals: we placed the animals below the sensor on a small wooden table (guinea pig) or in open plastic containers (rabbit and hamsters) and waited about 1 min to let them relax before we started the measurement. The mouse was measured in an anesthetized state. The MCGs were averaged before further analysis. We determined QT intervals, RR intervals and the standard deviation of the RR-intervals as a measure for the heart rate variability. The acquisition software of the high-T_c system performs on-line averaging, that prevented us from determining RR values for the mouse MCG.

RESULTS

The MCG could be measured in all animals. The maximum QRS amplitudes were approximately 2 pT in the rabbit, 3 pT in the guinea pig and 300 fT in the hamsters. In Fig. 1, we present the raw data from 10 channels of the rabbit MCG. Due to the respiration artifact, the determination of QT interval measurements could only be performed in averaged data. The values for QT and RR intervals are resumed in Table 1.

Table 1. QT intervals determined from averaged MCG in the different species

Animal	rabbit	guinea pig	hamster #1	hamster #2	mouse
QT interval/ms	145	120	63	58	38
RR	273	240	92	115	n.a.
stddev(RR)	9	8	1	1.5	n.a.

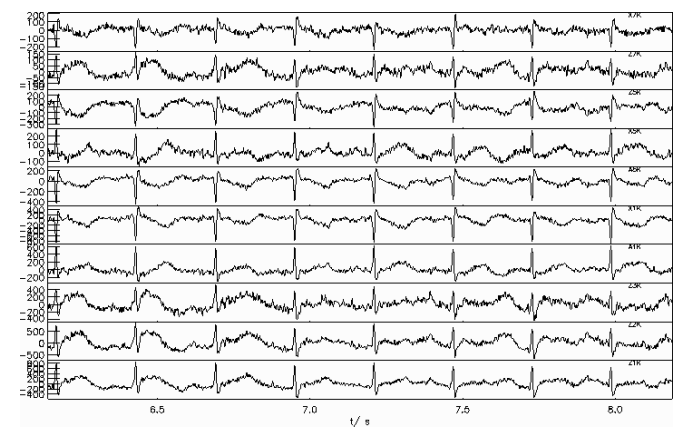


Fig. 1. 10 channels of a rabbit MCG, raw data. The QT intervals can only be determined after averaging.

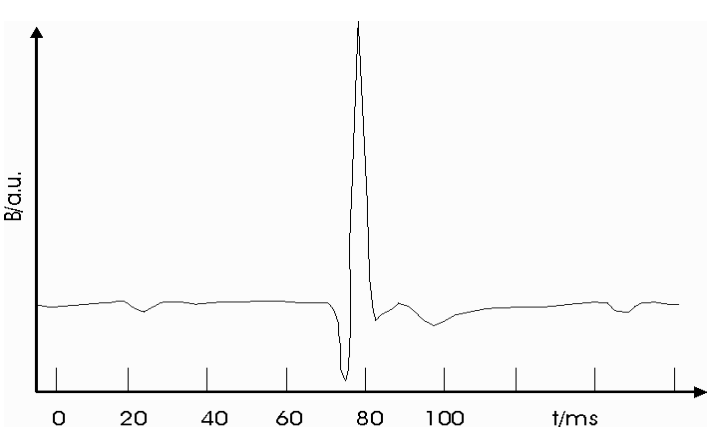


Fig.2. A mouse MCG acquired by a high-T_c SQUID system, the trace shows averaged data.

From the measurement experience and from previous theoretical considerations we developed a concept for an animal MCG device. The system will be adopted for measurements on conscious or anesthetized mice and rats. The animals will be placed in a room temperature bore inside the dewar. Conscious rodents tend to relax in a narrow and dark environment, which will improve the signal quality. The animal is surrounded by SQUIDS to acquire comprehensive field information. A superconducting niobium shield immersed in the liquid helium will avoid the need for operating in a shielded room.

DISCUSSION

We demonstrated the feasibility of QT interval and heart rate measurements in conscious unrestrained small animals. MCG might thus be used as an alternative to labour-intensive telemetric methods. The ease of the MCG measurement procedure opens possibilities to increase safety margins by better statistics due to the involvement of a large number of animals in pre-clinical studies. We showed that also high-T_c SQUID systems can be used to perform such studies. An MCG device especially designed for animal studies will be a useful tool both in drug safety investigations as well as in knockout model phenotyping. The construction of such a special system is currently prepared at PTB.

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An imaging and quantitative analysis technique for diagnosis of electro-physiological excitation abnormality of heart

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ABSTRACT

We describe two novel methods for characterization of the electrical cardiac propagation pathway using imaging techniques and quantitative analysis. A visual representation of the cardiac current distribution regions was constructed by superimposition of the frontal and posterior magnetocardiogram on the anterior and posterior standard heart shapes to produce a projected current arrow map (pCAM). Further, quantification analysis was performed using a dual current-vector diagram (dCVD). Time changes in the magnitude of each maximum current vector on both current vector maps were traced on the dCVD. These techniques were applied to patients with heart disease and yielded good characterization of the abnormal cardiac propagation pathways.

KEY WORDS

Magnetocardiogram, Arrhythmia, imaging, Atrial depolarization, Ventricular depolarization

INTRODUCTION

Magnetocardiogram (MCG) analysis of cardiac electro-physiological excitation using a single dipole model is limited in that it can only estimate the pre-excitation region in the context of Wolff-Parkinson-White (WPW) syndrome or premature ventricular contractions (PVCs). Because abnormal cardiac electro-physiological phenomena are normally widespread, analysis methods using the current distribution are required for appropriate application of the MCG to various states of heart disease, including arrhythmias and ischemia. We previously described a current arrow map for this purpose using tangential components that are directly measured or derived from differential normal components in the x- and y- direction. Use of the current arrow map allows for characterization of the widespread and/or multiple activated regions by assessment of the anterior and posterior heart, which can not otherwise be analyzed by electrocardiogram (ECG).

Despite this technique, it is still difficult to determine the relationship between heart position and the sensor coordinate, as the current arrow map does not reflect heart position directly. We previously described a MRI-acquired 3D standard heart model used to develop a projected current arrow map (PCAM), which allows superimposition of the current arrow map on the standard heart model. These time sequential maps facilitate visual characterization of the electrophysiological propagation. However, diagnosis of any abnormalities using these images is a subjective process and requires several maps during each observation interval. Therefore, development of a simple quantitative analysis method would be of benefit for practical clinical diagnosis using the time sequential images. The present report describes the use of a dual current vector diagram (dCVM) to extract the quantitative cardiac propagation characteristics and applies this technique to test cases of arrhythmia.

METHODS

Measurements were performed at the University of Tsukuba using a Hitachi magnetocardiograph (MC-6400) with 64-channel coaxial gradiometers. The sensor array is composed of an 8 x 8 grid of sensors with a 175 x 175 mm² measuring area that encompasses the adult whole heart. The measurement of anterior and posterior MCG was performed on subjects in the supine and prone positions, respectively, with adjustment of the sensor position to the same heart area. These data were analyzed by the projected current arrow map (PCAM) and dual current vector diagram (dCVD). The standard heart model was constructed from MRI of healthy men and was used for the heart shaped current arrow map. Time axes of the frontal and posterior MCG were adjusted using the reference signal of concomitant electrocardiogram. The current arrow map was obtained by calculation of the tangential components from the differential of measured normal components in the x- and y-direction and was superimposed on the standard heart model. The dCVD consisted of tracings of two parameters of maximum current vector strength and direction at each measured planes. The direction angle was adjusted to the same direction of vector electrocardiogram, with the positive direction of x-axis designated as $\theta=0$, and the clockwise direction designated as positive. Measurements were compared between normal subjects and patients with bundle branch blocks.

RESULTS

Analysis of normal hearts showed ventricular septum activation at the beginning of QRS complex, followed by right and inferior current flow and left ventricular activation. The PCAM at the R peak in normal subject is shown in Fig 1(a). The arrows in the figure reflect current intensity and direction at each measured position. The most activated regions at the R peak were in the left ventricle in the anterior and posterior maps, and the electro-physiological propagation was directed toward the left inferior region in each map. In contrast, in patients with right bundle branch block, activation initiated in the posterior heart at the beginning of the ventricular depolarization process. Further, the most activated times were not coincident in the anterior and posterior MCG, and the posterior peak was delayed compared with that of normal subjects, with the electro-physiological propagation of the anterior heart directed rightward (Fig. 1b).

Differences in the propagation process between the normal heart and the complete bundle branch blocks were compared using dCVD (Fig. 2). Two maximum current intensity curves of the QRS complexes in the diagram were obtained from the anterior and posterior heart. The current intensity related to the tangential magnetic field strength of the anterior heart was larger than that of posterior heart in normal subjects. Further, there were a few peaks in relation to the Q, R, and S peaks of the anterior heart, and the maximum peaks in both diagrams were nearly coincident. However, the strength of anterior heart with complete bundle branch block at R peak time was weaker than that of posterior one, and peak time was approximately twice that of the normal heart.

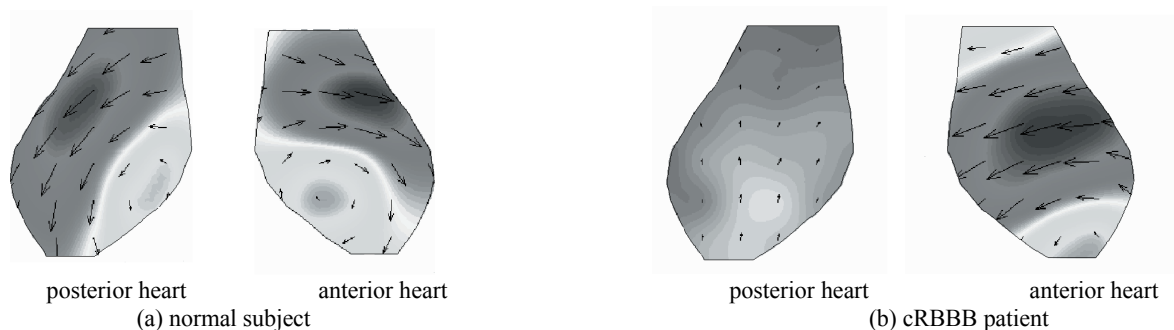


Fig. 1 Projected current arrow maps at maximum peak waveform during ventricular depolarization.

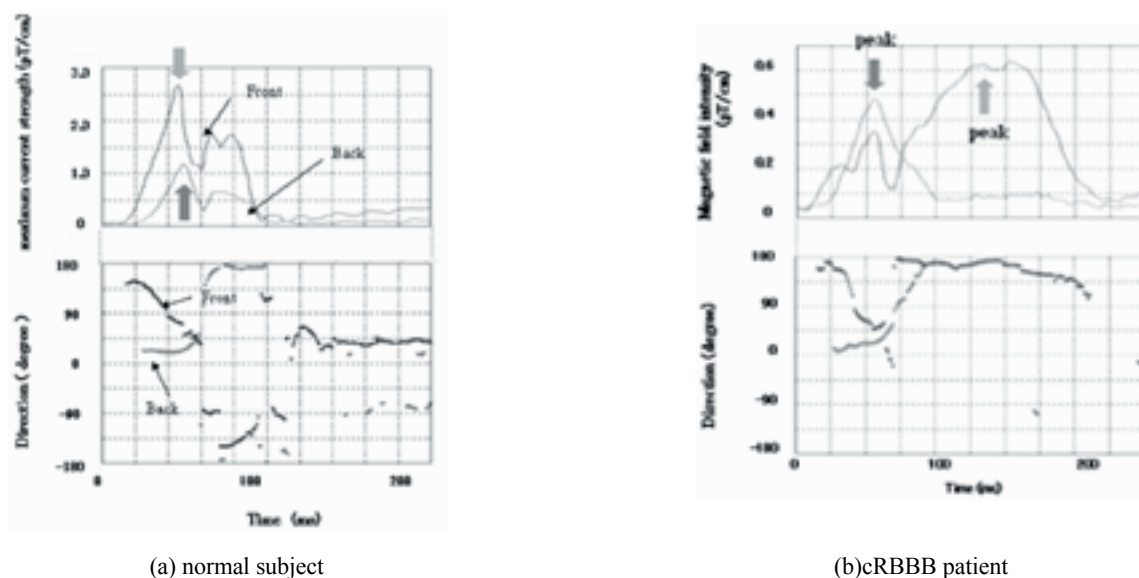


Fig. 2 DCVDs during ventricular depolarization.

DISCUSSION

The anterior and posterior pCAM allowed for visual inspection of electro-physiological propagation in heart muscle. Time sequential propagation changes during the QRS complex were easily observed, and differences between patients with normal hearts and those with bundle branch block were recognized. For example, hearts with right bundle branch blocks showed posterior left ventricle activation followed by activation of the anterior heart, and dCVD revealed prolonged excitation time and a change in propagation direction. These findings were consistent with changes in the pCAM. Thus, the pCAM is convenient method for visual inspection of widespread conduction abnormalities and electro-physiological excitation of the whole heart. Further, dCVD using current vector intensity and angle can objectively and quantitatively characterize the conduction process and avoid the limitations of the dipole model.

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3-D Magnetic Measurement of Exercise-Induced MCG

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ABSTRACT

We carried out a three-dimensional (3-D) vector measurement of exercise-induced magnetocardiograms (MCGs) for normal subjects with a wooden and brass-based bicycle ergometer. MCGs were measured by a 3-D second-order gradiometer connected to 39-channel SQUIDS, which can detect magnetic field components perpendicular to the chest wall (Bz) and tangential to the chest wall (Bx, By) simultaneously. Time-frequency analysis was applied to rest times and exercise-induced MCG data. It was shown that the power spectrum of the ST segment was different between the rest times and exercise-induced MCG. Principal component analysis (PCA) was also applied to the result of time-frequency analysis and the time course of frequency for the ST segment was evaluated quantitatively. It was found that dominant frequency of the ST segment in the rest time was ranged 5.5 to 6.5 Hz in all components. And it was clearly shown that the peak frequency of the exercise-induced MCG was shifted to 10.5 Hz compared to that of rest MCG.

KEY WORDS

Three-dimensional (3-D) exercise-induced magnetocardiogram (MCG), Time-frequency (t-f) analysis, Principal component analysis (PCA), QRS complex, ST-T segment, Target heart rate (THR).

INTRODUCTION

Biomagnetic field measurement is widely used the magnetic field perpendicular to the body surface. There are a few reports concerning with a 3-D vector measurement [Kobayashi K, 1998, Burghoff M, 1999]. We have developed a 39-channel SQUID system consisting of 3-D second-order gradiometers (12 measurement position (4×3) and a noise measurement) for vector measurement of MCG and magnetoencephalogram (MEG) [Uchikawa Y, 1999]. This SQUID magnetometer can detect magnetic field components perpendicular to the chest wall (Bz) and tangential to the chest (Bx, By) simultaneously. The MCG data of normal subjects or cardiac patients have been investigated both at rest and under conditions of dynamic stress [Hanninen H, 2000]. Most of them were reported about spatial distributions of the MCG data. And only a few study [Kobayashi, 1999] reported about a frequency change of the QT segment. We developed a wooden and brass-based bicycle ergometer for exercise-induced MCG measurement in magnetically shield room (MSR). The aim of this study is to investigate frequency change of the ST segment in exercise-induced MCG of normal subject using a 3-D vector MCG measurement system.

METHODS

A 3-D vector measurement of exercise-induced MCGs for eleven male normal subjects was performed by a bicycle ergometer made of wood and brass. The MCG and the ECG (lead II) was measured simultaneously, and all subjects had no history of cardiovascular disease, or signs of abnormalities in their ECG. The exercise-induced 3-D MCG measurement was done inside a MSR in all measurement. The MCG measurement of resting times was performed by first 4 minutes. Target heart rate (THR) for each subject, which is caused by exercise stress, was calculated using an equation represented by $THR = (220 - age) \times 0.85$ [kawakubo, 2000]. After reaching the THR, exercise-induced MCG measurement for ten minutes was carried out as shown in Fig.1. The exercise-induced MCGs filtered with from 0.5 to 300 Hz were sampled with 1000Hz. All magnetic data were averaged for 10 MCGs with same heart rate. The reference signal for averaging was the R-wave of ECG and digital filter was used in the range of 1 to 40 Hz.

RESULTS

Fig.1 shows an example of time course of heart rate during a measurement of exercise-induced MCGs. Target heart rates of all subjects were set by 166.6 to 168.3 [times/min]. Fig.1 shows an averaged heart rate by the eleven subjects. Heart rate of HR1 (after 5 [sec] from starting exercise-induced MCG measurement) was 160 ± 5.1 [times/min] and heart rate of HR2 (after 240 [sec]) was 100 ± 10.1 [times/min]. It was found that heart rate from HR1 to HR2 was sharply decreased, but it was as steady after HR2. Fig.2 shows typical MCG superimposed with all measurement points (48 channels). It was clearly shown that the ST segment of HR1 was short compared with the rest in all components.

DISCUSSION

The AR model [Vila J, 1997] was applied to the time-frequency (t-f) analysis of the MCG waveforms, with a time window (100ms) and was shifted every 5ms in analysis. The order of AR model was decided by final prediction error criterion (FPE) between 15 and 20. The short-time spectrum is calculated by equation (1).

$$B(f) = \frac{\sigma_e^2 \Delta t}{\left| 1 + \sum_{k=1}^p a_k^p \exp(-j2\pi f k \Delta t) \right|^2} \quad (1)$$

here $B(f)$ is power spectrum of MCG, σ_e^2 is variance of white noise, a_k^p is coefficient of AR model, p is order of AR model, and Δt is sampling time interval. The PCA was applied to the result of t-f analysis. Three different phases of the ST segment were analyzed in the analysis (I to III in

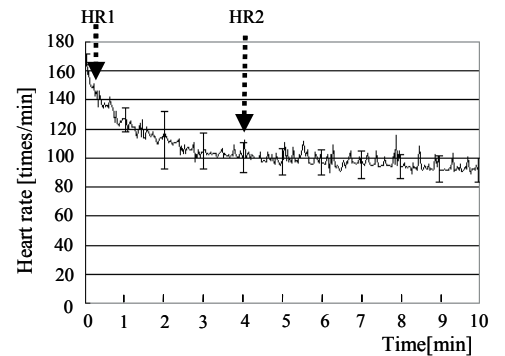


Fig.1 Time course of heart rate during exercise-induced MCG measurement.

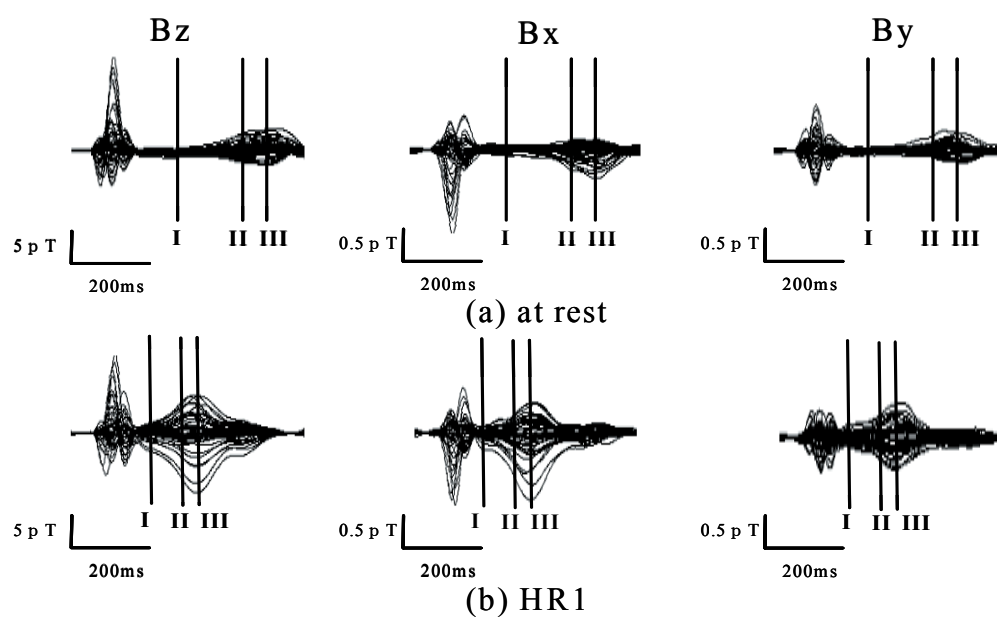


Fig.2 Examples of superimposed waveforms at rest and exercise-induced MCG measurement.

fig.2). Table.1 shows frequencies and score proportions of first principal component at rest and HR1 of three different phases from I to III. In HR1 just after reaching THR the dominant frequency of phase II was shifted 10.5 Hz from 6.5 Hz of Bz, 5.5 Hz of Bx, and 6.0 Hz of By in each component. And each score proportion of Bx and By was inverted compared to that of rest MCG. Dominant frequencies of phase I and III in both of at rest and HR1 were ranged 5.5 to 6.5 Hz in all components. A 3-D vector MCG measurement is useful for detecting frequency change of the ST segment in exercise-induced MCGs.

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phase		component	Bz	Bx	By
I	□ □ □	Frequency [Hz]	6.0	6.0	6.0
		Score proportion [%]	21.2	7.9	6.4
II	□ □ □	Frequency [Hz]	6.5	5.5	6.0
		Score proportion [%]	21.3	11.9	13.5
III	□ □ □	Frequency [Hz]	5.5	6.0	6.0
		Score proportion [%]	29.1	18.6	13.8

(a) at rest

phase		component	Bz	Bx	By
I	□ □ □	Frequency [Hz]	6.0	6.0	6.5
		Score proportion [%]	13.8	9.1	7.6
II	□ □ □	Frequency [Hz]	10.5	10.5	10.5
		Score proportion [%]	22.1	19.1	16.7
III	□ □ □	Frequency [Hz]	5.5	5.5	6.0
		Score proportion [%]	38.8	15.4	7.6

(b) HR1

Table 1 Frequency and score proportion of maximum value of the first principal component at rest (left panel) and HR1 (right panel).

New Computerized Methods for Current Density Vector Map Evaluation

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ABSTRACT

Objective and repeatable analysis for map evaluation is an obligatory requirement for a wide clinical acceptance of magnetocardiography (MCG). The aim of the present work is to develop two computerized classification systems for the current density map analysis, based on different principles, and check the usefulness of these systems for map classification in “difficult-to-diagnose” coronary artery disease (CAD) patients in comparison with healthy volunteers. The first system utilizes a topological approach and includes the following parameters of the map structure: number, intensity and orientation of the source fronts as well as asymmetry and ellipticity of the current vortexes. These parameters are combined in a single diagnostic index. The second system is based on analysis of the vector field of the current density maps and estimates direction and specific clusters of the vectors, which are also combined into a diagnostic index. To test these classification systems a group of 123 patients with proved CAD but normal or unspecifically changed resting ECG and normal EchoCG and reference a group of 124 healthy volunteers underwent MCG examinations by means of 4-channel magnetocardiographic system (MaGic, Magscan GmbH, Germany), installed in unshielded location. The topological method was proved to ensure high sensitivity, whereas the vector method was shown to provide high specificity in classification of the patients, i.e., the methods supplement each other. Therefore, a collective decision rule was developed based on the cut-off values of the indices. A combination of two approaches allows to approach 78% sensitivity and 82% specificity. Using the software package combining these two fully computerized methods could make analysis of magnetocardiographic data more acceptable for clinical routine.

KEY WORDS

magnetocardiography, current distribution, diagnostics, software system

INTRODUCTION

Nowadays, the method of magnetic field measurements (MCG) [Cremer, 1999] for investigation of the human heart bioelectrical activity is often used for diagnostic of pathologies. This raw information is yet not suitable to derive a medical conclusion because of magnetic field is caused by primary electric currents in the heart and, besides, the noise level of signal is too high. To reconstruct distribution of the current density from the known magnetic field configuration, it is necessary to solve the reverse problem in the theory of the stationary field. Localization of the current sources and imperfections of the conductive medium is a next step in a reverse problem solution. Solution of such a problem would be a considerable step forward in the investigation of the cardiac electrical activity. Apparently, diagnostic systems based on the objective data on the currents distribution and tissue conductivity could serve as a background for more reliable medical conclusions compared to the routine methods. In the present work based upon the existing understanding of the current initiation in the cardiac muscle, the models are considered for current spreading in a healthy heart (ideal distribution) and upon pathological alterations, characterized by additional distributed sources (or fronts of the sources) as well as by the heterogeneous conductivity. A final objective of the research is an elaboration of the tool for the diagnosis of heart injuries, especially the most common and severe. Thereupon, the paper analyses the results of application of the methods in computerized system and diagnostic of patients with verified coronary artery disease (CAD).

METHODS

Two systems for the description of the current density maps were elaborated: the system based on topology method [Vasetsky, 2002] and on vector field analysis. Both systems form numerical indices for deviation of the maps from the normal ones, with values of the indices being normalized to the interval $[0,1]$, at that the higher the magnitude of the index corresponds to the more deviation from the normal map. To receive comparison characteristics, the concept of the „ideal“ map is being utilized. As an ideal the current distribution, map is taken that has a dipole structure with two symmetrical current vortexes, created in a uniform conductive medium by a single sources front with a vector of current density (front direction) oriented to the left bottom from the patient viewpoint (or to the right bottom at the map) in the angle range $10^\circ\text{--}80^\circ$, counted clockwise from the horizontal axis of the map.

In the topology method the following four parameters of ideal properties of maps are used: R_f (characterizes presence or absence of additional sources), R_{dir} (determines deviation of the front direction from the ideal one), R_{as} (shows the degree of the current vortex asymmetry), R_{ell} (characterizes an ellipticity of the current vortexes). All parameters are consider to be independent. Parameters of the dipole structure R_f and direction P_{dir} play a decisive role in the classification system, two others, P_{as} and P_{ell} , are subsidiary ones. Summarizing R_{ideal} parameter includes four R_i parameters. Equation that combine this requirements is used as following: $R_{ideal} = R_f R_{dir} W + R_f R_{dir} R_{as} R_{ell} (1 - W) = R_f R_{dir} [W + R_{as} R_{ell} (1 - W)]$, where W is weight of the main parameters. Supplemented parameter $K_{ideal} = 1 - R_{ideal}$ characterizes the degree of deviation of the map from the ideal one. Finally, mean value $\bar{K}_{ideal}$ of index of map deviation from the ideal one is calculated at the S-T interval of the cardio cycle.

In the vector method processing of every map is reduced to the following steps: conversion of the coordinates of density current vectors $\vec{j}_{ij} = (x_{ij}, y_{ij}) \Rightarrow \tilde{\vec{j}}_{ij} = (l_{ij}, \alpha_{ij})$, where $l_{ij} \in [0,1]$ is a module and $\alpha_{ij} \in [0,2\pi]$ is a direction; definition function of belonging to the ideal direction b_{ij} ; isolation of the clusters with groups of vectors, which meet the condition $b_{ij} l_{ij} \geq l_0$, here l_0 is a constant defined by an expert; definition of a $C_m \in [0,1]$ index, characterizing closeness of the m -map to the „ideal“ one and calculation the mean value $\bar{C}_{ideal}$ for all M maps at the S-T interval.

COMPUTERIZED SYSTEM FOR PROCESSING OF MCG DATA

Suggested classification systems are constituents of the integrated software MAGWIN, providing analysis and interpretation of the magnetocardiograms in clinical conditions. The architecture of the system is represented in Fig. 1.

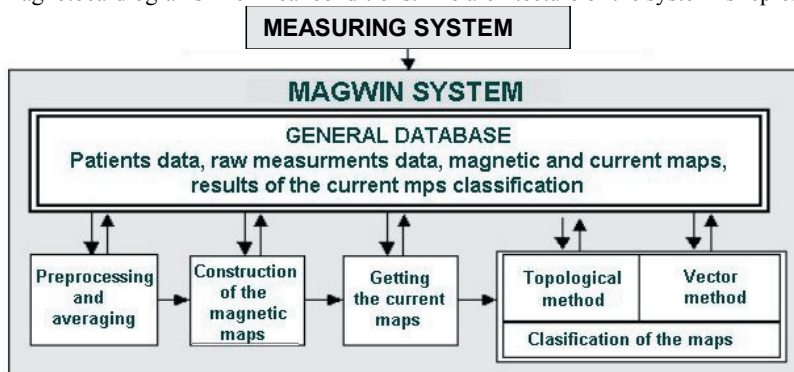


Figure 1. The architecture of the computerized system MAGWIN.

Subsystem for classification of the current maps consists of two parts, utilizing topological and vector methods for getting classification parameters, at that, each system operates independently from another. With topological method, the program generates predetermined number of the consecutive current maps displayed at the screen as level lines or vector field of the current density (Fig. 2) and generalized parameters of all maps in the chosen interval of the cardio cycle. Results of the maps classification by means of the vector method are represented in a special window of the system, providing not only graphical and textual information of interest, but also possibility to modify parameters used in the algorithm of the current density maps classification (Fig. 3).

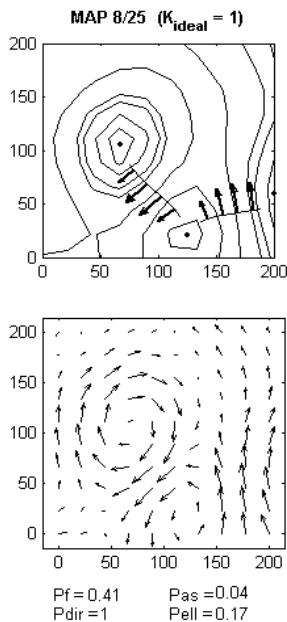


Figure 2. Current map and its parameters in topology method.

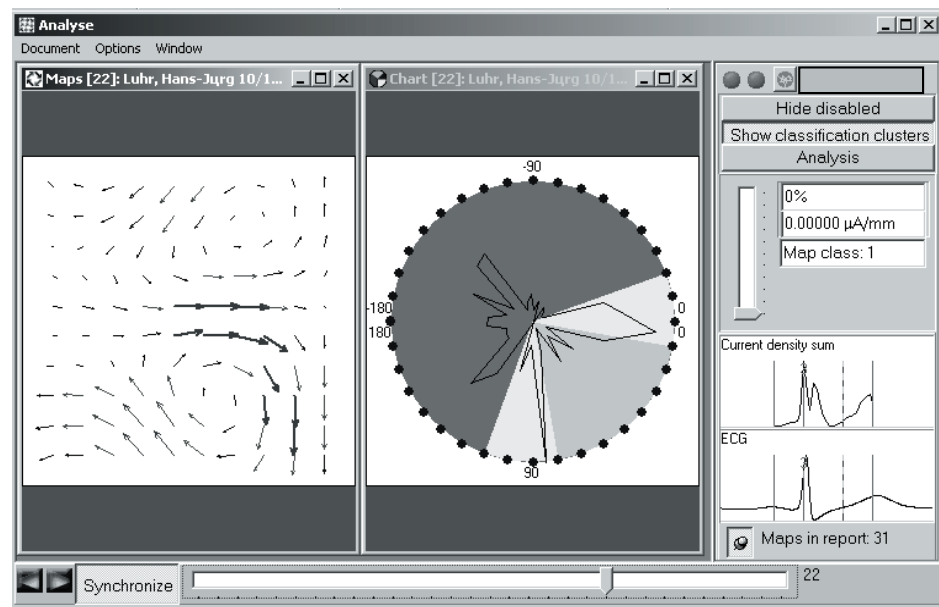


Figure 3. Graphical interface of the vector system for interpretation of the maps.

Testing of the suggested classification systems was performed on MCG data obtained in two samplings. The first group included 123 patients with diagnosed coronary artery disease (CAD), but normal or specifically unchanged rest ECG. Reference group consisted of 124 clinically healthy volunteers. The classification parameters of the topological method provide high sensitivity $S_E = 0.87$, whereas parameters of the vector method result in high specificity $S_P = 0.87$. In this respect, both methods, being realized in the unified computerized system MAGWIN, supplement each other. Depending on the aims and conditions of the diagnostics preference can be given to one of the methods.

DISCUSSION

On the base of suggested approach, collective decision rule can be developed, integrating partial solutions of the methods [Fainzilberg, 2002]. Classification parameter combining positive features of both methods seems to be even more perspective. Very promising could be also combined analysis of the primary parameters of maps description, reflecting positive features of both methods. Such classification system could approach the sensitivity of the topological method and specificity of the vector method.

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Comparison of magnetocardiographic and electrocardiographic abnormalities in closed chest pigs with chronic ischemia

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The aim of this study was to compare the degree of electrocardiographic abnormalities to the degree magnetocardiographic produced by chronic ischemia in closed chest pigs.

Methods: 8 sedated pigs (were transferred into the mobile MCG unit. All pigs underwent permanent LAD flow reduction 8 weeks before measurement. MCG was recorded by means of the 4-channel MCG system (MCG 7, Magscan GmbH, Germany) installed in a unshielded location. Based on the magnetic field distribution 20 subsequent current vectors maps were reconstructed with equidistant time step within the ST-T interval. Every single current vector density maps were classified by one of the 5 classes (0 reflecting fully normal distribution, 4 reflecting highly pathological distribution). The classification is mainly based on the dipolar or non-dipolar structure of the maps and the direction of the largest current density vectors. In addition 12- leads ECG was recorded in every pig. T-wave abnormality categories were evaluated in accordance with method proposed by Jacobsen et al.[1].

Results: All 8 pigs shown pathologic current distribution (class 3 and 4) within the entire ST-T interval.

In contrast one or more category of T-wave abnormality were found in 4 pigs only. Any electrocardiographic signs of ischemia were found in 4 other pigs.

Conclusion. MCG seems to be more sensitive to chronic ischemia than ECG in closed chest pigs.

[1] M.D. Jacobsen, G.S. Wagner, L. Holmwaag et al. Clinical significance of abnormal T-waves in patients with non-ST-segment elevation acute coronary syndromes. Am. J. Cardiol. 2001; 88,1225-29

Effects of imaging area in the identification of electrical propagation in atrial tissue using a multichannel SQUID system

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Magnetic field measurements of isolated rabbit hearts during normal cardiac rhythm were performed by a 16-channel SQUID system distributed on a 3.2 x 3.2 cm² area. Although the spatial resolution of the system is adequate, former work has pointed out to the necessity of increasing the mapping area in order to measure the whole relevant magnetic field. The present work compares the magnetic field map obtained with a grid that covers exactly the tissue sample area, with a grid three times larger than the tissue. In order to enlarge the mapping area, the sample was shifted over nine adjacent positions on a 3 x 3 square grid, yielding a total of 144 measurement positions. Electric potentials were recorded by a 4 x 4 array of silver electrodes (1 mm spacing between electrodes) placed on the surface of a small area of the heart tissue and were used to synchronize the magnetic recordings. Contour plot analysis showed that, although the sensor was very close to the tissue (1.5 cm liftoff), the distance between magnetic field extrema was still larger than the sensor array size, which comprised almost exactly the heart tissue limits. Analyzing the single-dipole inverse problem solutions, the results showed experimentally the effect of the magnetic field mapping area on the identification of the electrical activity propagation in heart tissue and identifies a relation of 3:1 as an adequate proportion of the mapping area to the projected bioelectrical source area.

This poster will be also presented in Workshop 4. For the full paper, see Page 93.

Magnetic Noise Reduction in Magnetocardiography Using ICA

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We introduce a spatial filter design method to reduce magnetic noises in magnetocardiogram (MCG). Based on the fact that external magnetic noises appearing on the multi-channel MCG sensors are independent of the cardiac signals and they have strong spatial correlation among the channels, we applied the independent component analysis (ICA) method to extract the noise components from the measured MCG signals. After extracting the noise components in a given time period with ICA, we made a spatial filter to reduce the noise components in the MCG signals to be acquired later on. MCG signal recordings have been performed with applying a low-pass filter of 100 Hz bandwidth to a 61-channel MCG-system. All the SQUID sensors of the MCG system sensitize the z-component of the magnetic field (the component perpendicular to the chest plane). Each SQUID sensor has a first order gradiometer configuration with the diameter of 21 mm. The SQUID sensors are arranged in a hexagonal array on a circular plane with the diameter of 23.5cm. The MCG system is placed in a magnetic shielding room (MSR) with the size of $2.2 \times 1.5 \times 2.0$ m³. In spite of the MSR, the MCG signals have been often corrupted by external magnetic noises coming from nearby electronic appliances and building vibration. In the experimental studies of 9 healthy volunteers, the spatial filters improved SNR of the MCG signals about 500% on an average. We expect that the spatial filtering method can be used for measurements of MCG signals in a magnetically noisy environment.

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Signal Space Separation in Magnetocardiography

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Signal space separation (SSS) is a new method utilizing two independent harmonic function (multipole) expansions for dividing multichannel biomagnetic recordings into separate components [1]. One component contains the biological signals (region I), and the other one represents the signals from environmental sources (region III); the sensors are in a source-free volume (region II). We applied SSS in magnetocardiographic (MCG) recordings of three healthy volunteers with a 99-channel cardiomagnetometer (Elekta Neuromag Oy). Excellent suppression of external disturbances was achieved. The expansion of the biological component was utilized in converting averaged MCG data into 49 axial gradiometer signals corresponding to the multichannel magnetometer at Physikalisch-Technische Bundesanstalt (PTB) Berlin, Germany. The same subjects were also recorded at PTB, and comparison between transformed and measured 49-channel data yielded a correlation of 96% in all three cases.

The authors acknowledge the PTB for the permission to use their data.

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